Faculdade de Farmácia da Universidade de Lisboa

&

Instituto Superior Técnico da Universidade Técnica de Lisboa

Thesis for Master Degree:

NEW APPROACH FOR PROCESS VALIDATION INTEGRATED WITH THE LIFECYCLE OF A PHARMACEUTICAL PRODUCT

Dissertation supervised by Prof. Dr. Rogério Sá Gaspar

Marta Cristina de Matos Fernandes

MASTER IN PHARMACEUTICAL ENGINEERING

2010

ACKNOWLEDGEMENTS

I would like to thank Professor Rogerio Sá Gaspar, under whose supervision I developed this thesis. I have to thank for his motivation through difficult times, for his vision focused in the future and for believing in my competence.

I would also like to express my acknowledgement to Dr. António Barros, Qualified Person and to Dr. Paulo Amaral, Quality Director of Lusomedicamenta, for their valuable comments and for their committed collaboration in the development of this thesis in a rational and organized manner. It was a pleasure to work and learn from their experience in pharmaceutical industry.

My Master' colleagues, which I really liked to meet, for their companionship, for their support, for their joyful spirit (despite the stress). It was good to share the hardest times and learn with their different personalities and professional experiences.

Thanks to Gloria Falcão, Quality Supervisor in Lusomedicamenta, who did not let me to quit right in the beginning, when it seemed so difficult to conciliate family, work and classes to attend. She is still a professional reference everyday, for her exigency, rightness and leadership. Thank you for the support and help in the collection of raw data.

Best friends are always present, no matter the geographic distance between them. I would like to thank my friend Ana Duarte for reviewing the draft of this thesis and especially for her true friendship since ever.

Last, but most important, the foundation of all, my especial thank to my parents for their unconditional encouragement and my boyfriend, Sandro Campos for his constant emotional support, without which I would not have been able to achieve my purposes. They all show me every day what really matters and they are true masters when it comes to optimize life's processes.

ABSTRACT

In November 2008, United States Food and Drug Administration (FDA) has launched for public discussion the draft of the "*Guidance for Industry Process Validation: General Principles and Practices*" which will bring a new approach of the actual concept of process validation, toward the concept of product lifecycle time.

The subject of this thesis consisted in a review of the principles and procedures concerning to pharmaceutical process validation in compliance with the Guidance for Industry Process Validation: General Principles and Practices (draft launched by FDA in November 2008), integrating the principles of the normative from ICH Q8, ICH Q9 and ICH Q10 with the new guideline of FDA on pharmaceutical industry process validation. A new strategy for process validation is proposed, having in mind the need for design experiments on a Quality by Design (QbD) commitment and the principles stated for product quality lifecycle implementation (PQLI). This will be achieved through integration of knowledge and background data from Manufacturing, Quality Control, Quality Assurance and Process Development areas.

The industrial process of a commercialized product composed of a mixture of 4 active substances formulated in capsules was studied. Currently the manufacturing process consists of raw materials sieving followed by a blending stage, where all the active substances and excipients are mixed. The filling operation is performed in an intermittent motion capsule filler with a low output, and manual feeding by the operator. However, this industrial process presents a batch to batch content uniformity variability of some of their active substances in finished product analysis. Since this is a process of an existing commercialized product, the aim of this work was to propose a new approach for planning a process optimization with minimal changes and consequent process revalidation.

Following International Society for Pharmaceutical Engineering (ISPE) suggestion for Product Quality Lifecycle Implementation (PQLI), there was an

adaptation of a control strategy model to the process focused in this thesis. In this case, the implementation of a PAT system would be useful in the hopper of encapsulation machine, for verification of the content homogeneity of the powder mixture after gravimetric discharge. Raman spectroscopy could be an option as a PAT tool, complemented with IR spectroscopy.

Keywords: Process Validation, PQLI, gravimetric discharge, content uniformity, content homogeneity, FMECA, Quality by Design

RESUMO

Em Novembro de 2008, a United States Food and Drug Administration (FDA) publicou a primeira versão da "*Guidance for Industry Process Validation: General Principles and Practices*" , para discussão pública. Esta nova guidance consiste numa nova forma de encarar a validação de processo, relativamente ao conceito de ciclo de vida de um produto farmacêutico.

Este trabalho consistiu numa revisão dos princípios e procedimentos associados à validação de processos farmacêuticos de acordo com as sugestões apresentadas na primeira versão publicada da "*Guidance for Industry Process Validation: General Principles and Practices*" , em conjunto com os princípios definidos pelas normas ICH Q8, ICH Q9 e ICH Q10 para a validação de processos industriais. Este trabalho apresenta uma nova estratégia de fazer a validação de um processo, tendo em conta a necessidade de planear as experiências com base na perspectiva do Quality by Design e dos princípios estabelecidos para a implementação da qualidade no ciclo de vida do producto (PQLI). Esse objectivo foi conseguido mediante a integração do conhecimento científico e do histórico de resultados recolhidos por diferentes áreas como a Produção, Controlo de Qualidade, Garantia de Qualidade, e Desenvolvimento e Investigação.

O processo industrial estudado ao longo desta tese é de um produto já comercializado, que consiste numa mistura com quatro substâncias activas, formuladas como cápsulas. Actualmente, este processo de produção consiste na tamização das matérias-primas, seguida da fase de mistura, onde todas as substâncias activas e os excipientes são misturados. A operação de enchimento é realizada através do funcionamento intermitente de uma máquina de enchimento de cápsulas com um baixo rendimento e a alimentação da máquina é feita manualmente, por um operador. No entanto, este processo apresenta alguma variabilidade de uniformidade de conteúdo de algumas substâncias activas entre lotes. Como este processo é referente a um producto que já está a ser comercializado, este trabalho pretendeu essencialmente sugerir uma nova forma de

planear uma optimização do processo e racionalizar uma eventual revalidação do mesmo.

De acordo com a sugestão da Sociedade Internacional para a Engenharia Farmacêutica (ISPE) para a PQLI, fez-se uma adaptação do modelo da estratégia de controlo para o processo em estudo. Neste caso, a implementação de um sistema PAT no alimentador da máquina de enchimento seria interessante, para verificar a homogeneidade da mistura após descarga gravimétrica. A espectroscopia de Raman apresenta-se como uma opção possivel para o sistema PAT, complementada com a espectroscopia de Infravermelho.

Palavras-chave: Validação de Processo, PQLI, descarga gravimétrica, uniformidade de conteúdo, uniformidade de mistura, FMECA, *Quality by Design*

ABBREVIATIONS

ACPS - *Advisory Committee for Pharmaceutical Science*

ANDA – *Abbreviated New Drug Application*

API – *Active Pharmaceutical Ingredient*

APV - Association *for Pharmaceutical Technology*

ASTM – *American Society for Testing and Materials*

CADREAC - *Collaboration Agreement of Drug Regulatory Authorities in European-Union-Associated Countries*

CFR – *Code of Federal Regulation*

cGMP – *Current Good Manufacturing Practices*

CPMP - *Committee for Proprietary Medicinal Products*

CPP - *Critical Process Parameter*

CQA - *Critical Quality Attribute*

CU – *Content uniformity*

DOE – *Design of Experiments*

EFTA - *European Free Trade Association*

EMEA - *European Medicines Evaluation Agency*

EOQC - *European Organization for Quality Control*

EP – *European Pharmacopeia*

EU – *European Union*

FDA – *Food and Drug Administration*

FIP - *Fédération Internationale Pharmaceutique*

FMECA - *Failure Modes Effects and Criticality Analysis*

FR – *Federal Register*

FT-IR – *Fourrier Transform Infra Red*

FT-NIR - *Fourrier Transform Near Infra Red*

GAMP - *Good Automated Manufacturing Practice*

GMP – *Good Manufacturing Practices*

HACCP - *Hazard Analysis and Critical Control Points*

HBr – *Hydrobromide*

HCl – *Hydrochloride*

HPLC – *High Performance Liquid Chromatography*

IBC – *Intermediate Bulk Container*

ICH - *International Conference on Harmonization of Technical Requirements for the Registration for Pharmaceuticals for Human Use*

IPC – *In-Process Control*

ISO - *International Standardization Organization*

ISPE - *International Society for Pharmaceutical Engineering*

JP – *Japanese Pharmacopeia*

LOD – *Loss on Drying*

LM – *Lusomedicamenta*

M – meter

MA – Marketing Authorization

NDA – *New Drug Application*

NIR – *Near Infrared*

NMR - *Nuclear Magnetic Resonance*

NMT – *Not more than*

OOS – Out of Specification

PAR - *Proven Acceptable Ranges*

PAT – *Process Analytical Technology*

PDA – *Parenteral Drug Association*

PDG - *Pharmacopeial Discussion Group*

PERF - *Pan-European Regulatory Forum*

PIC - *Pharmaceutical Inspection Convention*

PIC/S - *Pharmaceutical Inspection Co-operation Scheme*

PLM – *Pharmaceutical Product Lifecycle Management*

PQ – *Performance Qualification*

PQAS – *Pharmaceutical Quality Assessment System*

PQLI – *Product Quality Lifecycle Implementation*

PQS – *Pharmaceutical Quality System*

PTPP - *Pharmaceutical Target Product Profile*

QbD – *Quality by Design*

QOS – *Quality Overall Summary*

RPN – *Risk Priority Number*

RSD – Relative Standard Deviation

SPC – *Statistical Process Control*

Spec.- *Specification*

TQM – *Total Quality Management*

UK – *United Kingdom*

US – *United States*

USP – *United States Pharmacopeia*

WHO – World Health Organization

CONTENTS

THE REGULATORY HISTORY AND REGULATORY REQUIREMENTS FOR PROCESS VALIDATION

The rise of validation as a concerning matter in pharmaceutical industry began in the late 1970s, but process validation started to be required by law since 1962 when the Kefauver-Harris Amendments to the Food, Drug & Coloring Act were approved with Section 501 (a)(2)(B). According to that section, process validation for drugs (finished pharmaceuticals and components) is a legally enforceable requirement, since "A drug (…) shall be deemed to be adulterated (...) if (…) the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess" [2]. By that time, the only way FDA had to prove that a process had not done what it was designed to do and a drug was adulterated, was to collect samples from the final product, perform their analysis and show deviations from the specifications [3]. This constituted a significant regulatory burden for FDA alone and gave space to several cross-contamination problems and other accidents related to drugs manufacture [4]. Those problems highlighted the need for relevant alterations in law and in 1963 the first Good Manufacturing Practices (GMP) regulations became effective. With those, FDA was allowed to expect a preventative approach rather than a reactive approach to quality control, and due to Section 505(d)(3) FDA was then allowed to withhold approval of a new drug application if the "methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug" were "inadequate to preserve its identity, strength, quality, and purity" [5]. This meant that the law stated that a pharmaceutical manufacturer had to follow the current Good Manufacturing Practices (cGMP) regulations, while FDA had authorization to inspect manufacturing facilities at least once every 2 years [3,6]. However, during the following decade, FDA had to confront with several incidents in which people were injured and even killed, cases where sterility was not verifiable for an entire lot and

there were significant content uniformity problems as a reflex of poorly controlled manufacturing process [3]. Those incidents refocused FDA's attention to process itself and the way it had been designed and evaluated from a quality assurance-oriented point of view, rather than just a quality control intention. In 1974, Ted Byers, a consultant and former FDA inspector, presented a paper entitled: "Design for Quality" where he described the need for adequacy of processes for the production of pharmaceuticals [6]. In 1978, Bernard Loftus, a former director of FDA, published another paper entitled "Validation and Stability" where he discussed the legal basis for the requirement that processes be validated [6]. At the same time, FDA published the "Current Good Manufacturing Practices in Manufacture, Processing, Packing and Holding of Human and Veterinary Drugs" [7] and according to those, control procedures should be established to monitor output and to validate performance of the manufacturing processes to identify causes for the variability in the characteristics of in-process material and the drug product. Those processes were supposed to include tablet or capsule weight variation and adequacy of mixing to assure uniformity and homogeneity, which are associated to variability in manufacture process. One of the most relevant aspects is a well chosen method for mixing to assure uniformity and homogeneity. Disintegration time and dissolution time and rate should also be taken into account, since they are usually influenced by the selection of ingredients in the product formulation. Clarity, completeness or pH of solutions, are other relevant outputs to monitor.

Quality control procedures for finished product testing should include specifications and performance characteristics, and selection of appropriate methodology, equipment and instrumentation to ensure that testing of the product meets specifications. Also important are the final product testing, using validated analytical and testing methods to ensure that finished product meets specifications [6].

At the beginning of the 1980's, Loftus defined process validation as a matter of common sense, that is, a manufacturer would have to prove that a process works for this can be considered to be validated. In his opinion, FDA was giving too much emphasis in "what to do" questions and low importance to "how to do it", leaving this last matter to the manufacturer alone [8]. In 1982, Ted Byers wrote an article on how

to organize validations and to maximize their benefits. He presented this as a matter of a team approach and showed the need to industry become closer to FDA for cooperative work when planning individual validation cases. Edmund Fry, director of Parenteral Drug Association (PDA) at that time, joined the team who was preparing the draft of the United States (US) Guideline of General Principles of Process Validation. While trying to answer some of the questions raised from industry in the last years, he underlined that guidelines were not mandatory but intended to propose one way to accomplish the objective of the law [3]. There were efforts to highlight the positive aspects of process validation, such as business aspects and the numerous benefits to the manufacturer. Nevertheless, John Sharp, Principal Medicines Inspector at the Department of Health in the United Kingdom (UK) in the 80's, had a very different opinion on this subject. Just before the Guideline of General Principles of Process Validation has been published, he criticized FDA and industry for putting aside the real fundamental of doing process validation, since it was becoming so full of demanding standards. He thought validation should be inversely proportional to the adequacy of product design, raw material control and other quality control aspects. For him, the main point was the hazard to the consumer that a failure in the process could represent [3].

Meanwhile in Europe was taking place, especially in the UK, a similar process around process validation regulations since the end of 1960's, leading to the clarification of validation requirements for submissions according to the state of industry and the stage of harmonization process. In 1968 new guidelines for sale and distribution of medicinal products were introduced in UK [3]. The World Health Organization (WHO) has been conceived since 1948 and it still has an explicit responsibility to promote initiatives directed toward international harmonization of standards wherever and whenever this is appropriate within the health sector. In 1969 the WHO has issued the *Guidelines on Good Manufacturing Practices for Pharmaceutical Products* in 1969 and revised them in 1975 and 1992. In 1970, the health authorities of ten of the member countries of the European Free Trade Association (EFTA) created the Pharmaceutical Inspection Convention (PIC), having as main goals the harmonization of GMP requirements across its member countries and the mutual acceptance of GMP inspections [6]. In 1971 there was the first edition of the Orange Guide, which was a guide for GMP, published by the Pharmaceutical

Inspection Convention (PIC). This guide already presented validation as a beneficial practice in industry, but only in the revisions of 1977 and 1983 process validation for sterilization, aseptic processing and non-sterile processes were included [3].

In the 1973, the PIC published the *Basic Standards for GMP for Pharmaceutical Products*, based on the WHO standard and national guidelines. From 1975 onward, through the Council Directive 75/319/EEC, the European Union (EU) requested experimental validation studies for a manufacturing process to be included in the application dossier wherever it is critical for the product. International bodies such as the Fédération Internationale Pharmaceutique (FIP) and the European Organization for Quality Control (EOQC) were the first outside the United States to show interest in the process of defining the main contents of the extension of GMP for nonsteriles manufacturing. In 1980 the FIP published the *Guidelines for Good Validation Practice*, which stated a definition for validation, the process validation importance in the development phase and in production phase, notions of validation of existing processes, revalidation and addressing responsibilities [6]. In that same year, the EOQC organized a seminar in Geneva, where the main subject was validation of manufacturing processes [6,9]. This seminar worked as a reminder for disturbing aspects occurring and stated some relevant thoughts to the future; For example, the organization of a validation program depended on the individual company, and retrospective validation was acceptable for nonsteriles products if there was data with statistical meaning for justify this option. The benefits of having a process validated should be taking into account, despite its inherent cost, for it will probably spare time with problems in quality control, investigations and corrective actions. Validation and quality control should be thought as having a balance between them. The regulatory guidance (in a suggesting way) should define what had to be defined, study and determined, while each company should decide how will plan the validation process, which could include challenging conditions to identify the critical variables of the processes for new products. Finally, revalidation of a process was an accepted idea, with its strong aspects, but there wasn't a general agreement about the idea of the triggering mechanism. This event was also the first one where subjects like qualification of process equipment and support system were brought to public discussion [6].

The International Association for Pharmaceutical Technology (APV), headquartered in Germany present in 1982 the seminar *Validation in Practice*, where speakers demonstrated how validation could be applied to industrial activities and how balance between resources allocation and results could be achieved. Validation was seen as just one tool in quality management. It should be gathered with acceptance testing, in-process and final control and the totality of the GMP. On the other hand, this seminar demonstrated validation should be adapted to the process and its objectives previously established. Each company should then be responsible for the extent, depth and way chose to do it. There was a new approach of validation since it was considered to be a demonstration that a process is under control, by monitoring certain conditioning variables lighted from the others by a risk assessment. Moreover, validation should consist in checks done routinely, with a frequency and type of analysis defined previously [6].

In May 1987 the "US Guidance on General Principles of Process Validation" was published, with intent to assist pharmaceutical, device and veterinary medicine industries. It has promoted the standardization of the approach by the different parts of FDA and it has been effective to communicate that to manufacturers in each manufacturing unit. Soon this Guidance became an important source of information to pharmaceutical manufacturers interested in establishing a process validation program. According to this guidance, "Process validation is establishing documented evidence which provides a high degree of assurance that a specific process (such as the manufacture of pharmaceutical dosage forms) will consistently produce a product meeting its predetermined specifications and quality characteristics" [10]. Assurance of product quality is derived, therefore, from careful and systemic attention to a number of important factors, such as selection of quality components and materials, adequate product and process design and control of the process through in-process and end-product testing. Thus, it is only possible to create a process with a high degree of confidence through careful qualification and validation of both process and its control systems, so that all individual manufactured units of a given batch or succession of batches that meet specifications will be acceptable.

The key steps considered, according to the 1987' FDA Guidance for Industry on Process Validation, for a completed product/process development program are presented in Table 1:

Development Stage	Pilot Scale-up Phase
Product design	1 x batch size
Product characterization **Product selection (formulation)** **Process design** **Product optimization**	10 x batch size
Process characterization **Process optimization** **Process demonstration** **Process validation program** **Product/process certification**	100 x batch size

Table 1 – The key stages in the product/process development sequence, according to 1987 FDA guidance, *as per* [6].

The reason why the end of the sequence has been assigned to process validation lies on the fact that the specific exercise of process validation shall never be designed to fail. Failing in the carrying out the process validation assignment is attributed to incomplete or faulty understanding of the process's capability. The major part of a process investment must be applied in process qualification in which the formalized final process validation sequence provides only the necessary process validation documentation required by the regulatory authorities, showing that the

manufacturing process is in state of control. Following this rational, an applicant firm under either a New Drug Application (NDA) or an Abbreviated New Drug Application (ANDA) submission would show, in a FDA's Preapproval Inspection Program, the necessary cGMP information and qualification data, together with the formal protocol for the approaching full-scale, and also formal process validation runs required before the product is launched.

The regulatory implementation of the validation requirement was also a deliberate process by FDA. Process validation was required, in both general and specific terms, by the cGMP regulations provided in 21 CFR parts 210 and 211 [11]. In section 211.100(a) the foundation for process validation was described, and according to it "[t]here shall be written procedures for production and process control *designed to assure* that the drug products have the identity, strength, quality, and purity they purport or are represented to possess" [12]. This meant that manufacturers had to design a process including operations and controls that would result in a product meeting these attributes. In this context of process validation, *product quality* concerns to product performance in a consistently way from batch-to-batch and unit-to-unit. Validation was also expected to offer assurance that a process was reasonably safeguarded from sources of variability affecting production output. In case of loss of that control, supply problems could happen for eventual negative effects on public health.

Many problems have been lighted up with continuous and widely spread inspections from FDA, until some of them end up in injunction cases contested in court. One of those cases, lead to some criticism pointed by the court itself to FDA, in respect to the lack of specificity and ambiguity and vagueness of the cGMP regulations. In response to that, FDA published in May 1996 a Federal Register where intended to emphasize and clarify the process validation requirements, including a definition of process validation, a specific requirement to validate manufacturing processes and a minimum requirements for performing and documenting a validation study [13]. There was nothing new comparing to the Guidance published on 1987, but an effort to specify what already was implicit since 1987. Regarding those revisions, there were many comments about the definitions and terminology proposed about which processes and steps in a process should or

should not require validation, the number of batches required for process validation, maintenance of validation records and the assignment of responsibility for final approval of a validation study and change control decisions [6]. This rule proposed in 1996 (61 FR 20103) has been withdrawal in 2007, since FDA has considered, at that time, it would be appropriate to newly evaluate the issues raised in that proposal [14].

In respect to sampling and testing of in-process materials and drug products, 21 CFR - section 211.110(a), states that control procedures must "(…) be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product" [11]. This meant that well-designed processes must include in-process control procedures to assure final product quality.

In section 211.160(b)(3) of the Act, cGMP regulations required that batch samples represent the batch under analysis and, according to section 211.165(c) and (d), the sampling plan must result in statistical confidence that the batch meets its predetermined specifications [12]. When establishing in-process specifications, there was two principles to follow (section 211.110(b)) [11]:

1) "(…) in-process specifications for such characteristics [of in-process material and the drug product] shall be consistent with drug product final specifications". This intended that in-process material should be controlled to assure that the final drug product would meet its quality requirements.

2) In-process specifications "(…) shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate." Accordingly, manufacturers had to analyze process performance and control batch-to-batch variability.

As far as process design, development, and maintenance were concerned, Section 211.180(e) stated that information and data about product performance and manufacturing experience should be periodically reviewed to determine whether any changes to the established process were warranted [15]. Ongoing feedback about

product performance was an essential feature of process maintenance, since the main purpose from now on was to do the PQLI in the process validation plan.

Facilities in which drugs were manufactured should be of suitable size, construction, and location to facilitate proper operations (21 CFR 211.42) [16], as well as equipment must be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use (21 CFR 211.63) [11]. There should be a written program designed to assure proper performance (21 CFR 211.68) of automated, mechanical, and electronic equipment, where was described the periodicity for calibrations, inspections and checking, with their results properly reported and archived [16].

Then in 1988, the guideline *Development Pharmaceutics and Process Validation* clarified what was expected to see in the application dossier: data describing the evaluation or validation of a manufacturing process [6]. In 1989 there was a revision where some definitions and requirements for validation were clarified, such as qualification and validation. According to this revision, qualification was the "action of proving that any equipment works correctly and actually leads to the expected results" [6,17]. The term validation was given as being the "action of proving, in accordance with the principles of GMP, that any procedure, process, equipment, material, activity or system actually leads to the expected results". This publication stated that:

- Validation studies should reinforce GMPs and be conducted according to them, with the respective results and conclusions recorded.

- A new formulation or method of manufacture must be put to test in order to demonstrate it was suitable for routine processing and to yield a product consistently with a required quality.

- Amendments to the process, such as change in any equipment or material, considered as relevant for the quality of the final product, should be validated.

- Periodic revalidation of processes and procedures should be done to ensure that they were still capable of lead to the required result.

These principles have remained until today unchanged in the PIC's Guide to Good Manufacturing Practice of Medicinal Products [17].

Looking back to Europe, in 1989 the first edition of the European Guide to GMP was published and outdated all national guidelines within EU [3]. This guide prepared by the European Commission together with the European Medicines Evaluation Agency (EMEA) guidelines, served as a model followed by all European countries whether or not from EU. There have been some updates along the years in respect to more precise guidelines and definitions for European medicinal industry up until recently, when systematic validation of all pharmaceutical manufacturing processes started to be seen as necessary.

During 1990's reactions to the 1987' US Guidance on Process Validation have come to public and other negative opinions about FDA guidance joined Sharp. The importance of patient perspective and how much validation was worth for patient and for the world, this is, there was not only a regardless treatment of the human point view but also of the economic and strategic impact of the process validation concept. There were comparisons of the expenditures on validations and their influence on prices of medicinal products with annual incomes of people in developing countries in need of those medicines [3]. In this sense, validation was becoming a negative force within the pharmaceutical industry and there was a need to change the way to approach its objectives. Instead of promote development, process validation seemed to promote the lackness of creativity among scientists and engineers.

More enthusiastic minds about the values of process validation and followers of FDA regulations, tried to underline that validation was nor supposed to be a regulatory burden and it should be defined as an application of total quality management (TQM), noting that quality of the validation was what really matters, not the quantity [3]. Even though, in 1995 Sharp's opinion was still opponent to FDA's approach to validation, with all its bureaucratic forms, and he said that all an inspector need to ask was the prove that a given process works, in that it achieves what it is intended to achieve [3]. More constructive critics to the US Guidance on Process Validation of 1987, brought the need for risk-benefit analysis and the need for remembering to consider human element when planning process validations, since the human intervention in processes represents a threat to sterilization and

stability of processes. At the same time, technology applied to industry was spreading and with it more skilled human resources became necessary and also a specific training for workers involved in process validation [18].

Specifically on process validation subject, in 1993 the WHO issued Annex 5 to its GMP guide: *Guidelines on the Validation of Manufacturing Processes*, where is explained the concept of validation and is shown the need for establish priorities and select some approaches for developing a validation program [6].

In 1995 the PIC become Pharmaceutical Inspection Co-operation Scheme (PIC/S) as a scheme operating as an informal arrangement between the national agencies of countries from European Economic Space (EU members, Iceland, Norway and Liechtenstein), and Third Countries, with the focus on harmonization of GMP, training of inspectors and development of guidelines. Actually it is constituted by 34 countries from all continents [19].

The medicines agencies of the eastern-European countries have associated as the Collaboration Agreement of Drug Regulatory Authorities in European-Union-Associated Countries (CADREAC), to establish a counterpart to the EMEA. The Pan-European Regulatory Forum (PERF) was created by the EU to make link between the East and the West and to promote good scientific practice. The main goals of this forum are to discuss GMP, pharmacovigilance issues and accession countries' progress in adopting the body of EU legislation [6].

Since 1996 the Japanese government stated the purpose of validation as being "to validate that buildings and facilities of a manufacturing plant and manufacturing processes and other methods of manufacturing control and quality control yield anticipated results, and to ensure the constant manufacture of products of intended quality by documenting such procedures" [6].

In 1998 new trends were being notice in pharmaceutical industry, as an increase of pressure for "do more with less" resources, improve quality with lower costs, the globalization of the pharmaceutical industry and an increase in contract manufacturing. In Europe, there were also several points of view about all the relevance of process validation, but most of them were positive and accepting its nature. Validation was mainly seen as a tool to achieve quality assurance, resulting

in reduced production and control of costs. All the guidelines should be accepted as a framework for process validation and give guidance to reasonable documentation practice, but for sensitive cases as cross-contamination prevention or aseptic preparations detailed instructions should be followed. In 2000 Canada contribute to this subject with *Validation Guidelines for Pharmaceutical Dosage Forms*, with a unique three parted way of seeing the validation process. They cover the all-encompassing activities with the identification of critical variables in the process, taking into account a worst-case scenario, through equivalence of final formulation, but they also restricted the validation process to the formal exercise of examining three batches at production scale [6].

Between 1997 and 2001, more detailed instructions were prepared and in 2001, the EMEA published the Annex 15 (Qualification and Validation) to the EU Guide to GMP [20]. In this same year, EMEA also published the *Note for Guidance on Process Validation* prepared by the Committee for Proprietary Medicinal Products (CPMP), for marketing authorization applicants [21]. At this time became clear that a process validation protocol should be included in the submission dossier. However, the amount of data from validation would depend on the nature and complexity of the drug substance, drug product and manufacturing process. In cases where production scale data are not available at the time of submission, validation can be performed in two steps: a detailed characterization of the critical process parameters at pilot scale, included in the dossier, followed by a formal validation program on production scale with the respective protocol included in the dossier [6]. There are few differences between the PIC/S *Recommendations on Validation Master Plan, Installation and Operational Qualification, Non Sterile Process Validation and Cleaning Validation* stated in 1999 [22], and the Annex 15 to the EU GMP guide issued in 2001. The PIC/S recommendations were written as instructions for the inspectors with the aim of establishing a common philosophy of the validation topics. The scope of Annex 15 was limited to drug products only (without active pharmaceutical ingredients (APIs)) and identified the risk assessment as an important tool in defining the elements and the extent of validation and qualification. The term *design qualification* was added and the expression *could* appear as an alternative to the usual *should* in this type of documents [6,17]. At the same time the Annex 15 was published, the Note for Guidance on Parametric Release was issued, which added more importance to

process validation. Looking at GMP today, there has been stated a clear similarity among the different countries in the world. For example, the EU GMP guide published in 2001 and the Australian guide from 2002 [23] onward are identical triplets of the PIC guide to GMP [6].

But one of the most important steps in harmonization of manufacture of pharmaceutical products around the world was the foundation of the *International Conference on Harmonization of Technical Requirements for the Registration for Pharmaceuticals for Human Use* (ICH), in 1990. This came from the intention of EU, United States and Japan to harmonize the regulatory guidelines in these three regions in order to reduce duplication and redundancy in the development and registration of new drugs [6, 24].

By 2002, process validation was seen as an integral part of quality assurance, as it consisted in the systematic study of systems, facilities and processes designed to determining whether they perform their intended functions adequately and consistently as specified. Thus, validation itself wasn't intended to improve processes but to confirm that processes have been developed effectively and were under control. There was already the intention to monitor the process continuously, though in practice this was still more an intention than a reality in most of manufacturers. Process validation could be performed in two ways: the experimental approach and the approach based on the analysis of historical data. In the experimental approach, which included the prospective and concurrent validation, there were an extensive product testing, simulation of process trials, worst case trials and control of process parameters. In the approach based on retrospective data, no experiments were performed, but instead an thoroughly evaluation of all historical data and then, the results including the outcome of process capability studies and trend analysis would indicate whether the process was under control or not [25].

In 2004, FDA challenged all industry's traditional approaches to ensuring product quality with the initiative "GMPs for the Twenty-First Century", focused on quality by design, risk management, continuous improvement and quality systems. One of the primary effects would be to encourage employees to look beyond traditional inspection methodologies in final quality control. Other aspect was the emphasis on the level of scientific knowledge and understanding of a manufacturing

process and the approaches chosen to ensure that a process is "validated" [26]. But this initiative brought to discussion the regulatory issue, since changes in a validated process, as is expected in a continuous improvement program or due to real-time-control or some improvement step incorporated in Lean philosophy or Six Sigma, seems to precede another stage of filling manufacturing supplements to regulatory entities. The question was the need of such bureaucracy and the extent of detail and implications of those improvements on product quality and respective registered file. Along with the Pharmaceutical GMPs for the Twenty-First Century initiative, FDA formed the Council on Pharmaceutical Quality, which has been taking care of all policy development, coordination and the implementation of specific quality management systems within FDA's operations [27].

Meanwhile, in May 2006 ICH has published the *Guidance Q8 Pharmaceutical Development* [28], which brought to public the intention of a new way of thinking in validation process along the development process of a product. That should be possible taking into account not only the knowledge about the quality desired for the final product, but also by understanding the process as well as all its raw materials attributes, in order to apply the principles of QbD. Process development studies should provide the basis for process improvement, process validation, continuous process verification (where applicable), and any process control requirements. According to ICH Q8 *Pharmaceutical Development,* information from pharmaceutical development studies can be a basis for quality risk management. It is important to recognize that quality cannot be tested into products, or in other words, quality should be built in by design. Changes in formulation and manufacturing processes during development and lifecycle management should be looked as opportunities to improve knowledge and further support establishment of the design space. Inclusion of relevant knowledge gained from experiments giving unexpected results can also be useful. Design space is proposed by the applicant and is subject to regulatory assessment and approval. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory postapproval change process. The basis for science-based submissions and their regulatory evaluation is the level of knowledge gained. Where appropriate, such studies should address microbiological as well as physical and chemical attributes. The knowledge gained from process development studies

can be used, as appropriate, to justify the design space, the drug product specification and manufacturing controls.

The ICH *Guidance Q9 Quality Risk Management* [29] has been published in June 2006, presenting risk assessment as a relevant tool for rational planning for processes in industry with more effective and consistent risk-based decisions, by both regulators and industry, regarding the quality of drug substances and drug products across the product lifecycle. This strategy allowed reducing the amount of tests and bureaucracy related to submission dossier and its requirements, because working with a correct risk management, a company can justify all its options taken along the process, being conscious of the eventual consequences during a manufacturing routine. Appropriate use of quality risk management does not minimize industry's obligation to comply with regulatory requirements. However, effective quality risk management can facilitate better informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks and might affect the level of direct regulatory oversight. Quality risk management should be integrated into existing operations and documented appropriately. While regulatory decisions will continue to be taken on a regional basis, a common understanding and application of quality risk management principles (ICH Q9) could facilitate mutual confidence and promote more consistent decisions among regulators on the basis of the same information.

Since December 2007, *ICH Q10 Pharmaceutical Quality System* has been available for discussion as a draft and the final version was published in April 2009 [30]. Based on International Standardization Organization (ISO) concepts, includes applicable GMPs regulations and complements *ICH Q8 Pharmaceutical Development* and *ICH Q9 Quality Risk Management*. ICH Q10 is a model for a pharmaceutical quality system that can be implemented throughout the different stages of a product lifecycle, so innovation, continual improvement and strengthen the link between pharmaceutical development and manufacturing activities can be possible. For the purposes of this guideline, the product lifecycle includes the Pharmaceutical Development and Technology Transfer. Knowledge management and quality risk management are enablers of ICH Q10 that facilitate a consistent scientific approach to achieve the objective of being in compliance to GMPs and

regulatory requirements needed for marketing approval. The quality systems approach describes the responsibilities of the quality unit, which combines the duties of quality control and quality assurance, ensuring that the various operations associated with all systems are suitably planned, approved, conducted and monitored [31].

With all this pharmaceutical globalization activities, the need for international harmonization of compendial standards for APIs and excipients was brought to discussion. The *Pharmacopeial Discussion Group* (PDG) was formed in 1989 as an alliance between the United States Pharmacopeia (USP), the European Pharmacopeia (EP) and the Japanese Pharmacopeia (JP). The harmonization effort includes monographs for individual excipients and also general tests, which lead to GMP and validation topics in the field of content uniformity and blend uniformity [6].

Another allied in this path for standardization of process validation is the *International Society for Pharmaceutical Engineering* (ISPE) which is a worldwide nonprofit society of technical professionals who apply their knowledge in the regulated health care technology manufacturing industries since 1996. The ISPE is responsible for the Good Automated Manufacturing Practice (GAMP) *Guide for Validation of Automated Systems*. This guide plays an orientation role to the suppliers of automated systems to the healthcare industries on the development and maintenance of all types of automated systems following good practice, helping to standardize validation concepts and approaches [6]. In July 2007, the ISPE launched the PQLI initiative in the United States and then, in September 2007, in Europe. The intention of PQLI is to work with industry and regulatory agencies worldwide to facilitate a common understanding of QbD and introduce practical means for the implementation of ICH's guidances (Q8, Q9 and Q10), based on engineering and business principles [32].

With worldwide expansion of pharmaceutical manufacturing there has been a desire for harmonized international standards and requirements. There has been also a growing effort to reduce the cost of process validation and incorporate validation consideration during product design and development, in a QbD sense along the lifecycle of a product. New technologies and innovations in pharmaceutical

industry may also have a relevant effect on process validations concepts and how they can be implemented and regulated in the future. The concept of GMPs has converged on the quality systems approach rather than having only a quality assurance supporting system. Validation has become accepted as a tool to be used with common sense, and risk assessment became an important core activity to control the extent and depth of validation. Process validation has become part of strategic quality management and performance improvement [3]. With all its benefits to patients as well as for manufacturers, the challenge is now to find the level of cost-effective validation without any risk for the consumers.

Published as a draft in November 2008, the new *Guidance for Industry Process Validation: General Principles and Practices* aligns process validation activities with the product lifecycle concept and with existing FDA guidance. The lifecycle concept links product and process development, qualification of the commercial manufacturing process and maintenance of the process in a state of control during routine commercial production. The quality assurance of a product incorporates the understanding that the following conditions exist:

- Quality, safety and efficacy are designed or built into the product;
- Quality cannot be adequately assured merely by in-process and finished-product inspection or testing;
- Each step of a manufacturing process is controlled to assure that the finished product meets all design characteristics and quality attributes including specifications.

According to this new guidance, process validation is defined as “the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products” [1]. During the lifecycle of a product, the process validation activities should be distributed in three stages:

Stage 1 – Process Design: in this stage the commercial process is defined based on knowledge gained through development and scale-up activities.

Stage 2 – Process Qualification: the process design is confirmed as being capable of reproducible commercial manufacturing.

Stage 3 – Continued Process Verification: during routine production, the process will be still verified, so that assurance is given in respect to the process state of control.

This guidance also reinforces the need for manufacturers know and understand the whole process and the sources of its variation, to detect the presence and degree of that variation, understand the impact of variation on the process and ultimately on product attributes and, finally, control the variation in a measurable manner, so that becomes possible to do a risk assessment of what that variation can represent to the process and the product. However, maintaining the process in a state of control over its lifecycle includes monitoring materials, equipment, production environment, personnel and manufacturing procedures change. The FDA new approach proposed for process validation involves a relevant economic and technological investment for a medium/long-term, but solid, capital return.

NEW CHALLENGES FOR PROCESS VALIDATION

Industry has been managed in a manner of quality by inspection, in a way where quality is verified in the final stage of the process development, or at least at the end of production line. This procedure has revealed itself as the source of many development-to-manufacturing issues due to poor quality performance. Although all the quality improvements that have been made along the last years, too much emphasis have been given to paper work and documentation, putting aside the true resolution for manufacturing problems and assurance of product quality. This approach has brought several economical and industrial problems, as far as it concerns to costs, robustness of processes, sustenance of such processes and adequacy for the emerging pharmaceutical products with complex and demanding features [33]. The need for inspection comes from excessive variability in a process and, to discard that variability, manufacturers need to understand the processes so well that can be possible to predict the quality of the final product, this is the output of a process, from upstream measurements and operations [34]. FDA's expectations are for industry to focus on reducing variability through process understanding, having product quality and performance guaranteed by application of a design of effective and efficient manufacturing processes, product and process specifications based on a mechanistic understanding of how formulation and process factors affect product performance and through the application of continuous real-time quality assurance [31].

According to the FDA's modern pharmaceutical manufacturing statements [35], the pharmaceutical industry can be summarized in five major topics:

- Effective and efficient manufacturing processes to promote and ensure product quality;

- Detailed understanding of the role of formulation and process elements into product performance and therefore, rational product specifications,

- Assurance of quality performed in real-time, continuously;

- Adjustment of regulatory policies to a specific product, according to its scientific complexity, its applications, process validation and process capability;

- Risk-based regulatory management is related to the severity with which formulation and manufacturing process can affect the final product quality, and also how process control strategies are able to prevent and mitigate the risk of producing a defective product.

Following these tendencies, pharmaceutical development and manufacturing will have to be associated to terms like QbD, scientific manufacturing and risk-based regulatory oversight. Recent guidance have been published in order to support and adjust the integration of these terms by manufacturers and subsequent implementation of a new system for process validation and routine manufacturing with an early and constant control strategy and less unpleasant surprises at a late phase of a given process. However, in spite of the way that implementation is performed is still a choice made by each manufacturer, the framework to QbD is explained in ICH Q8 and ICH Q9, while ICH Q10 provides the basis for pharmaceutical quality systems. The guidance Q8 promotes the collection of necessary knowledge and the ICH Q9 is about applying the collected knowledge to risk management. The ICH Q10 addresses the need for systems to maintain the process, the facility and the product quality throughout the product lifecycle [36].

To improve the predictability of a drug development and manufacturing processes, FDA's proposed a three-fold challenge to a risk-based framework for identifying, developing and manufacturing drugs, summarized in Figure 1.

Companies who proposed themselves to achieve these goals are subject to a complex process where they will have to reorganize their priorities, refocus their investments, plan of acquisitions in terms of equipments and technology, improvement of facilities, for which a "value-driven compliance" approach will be helpful and effective. This plan consists in five steps, centered in risk diagnosis, business refactoring, transforming industrialization, compliance-centric business architecture and compliance-centric Information and Technology (IT) architecture [37]. These five areas consist of an economic analysis together with an engineering

approach, in other words, a team work, where all the fundamentals of a company must be put to the test and readjust to future expectations of industry.

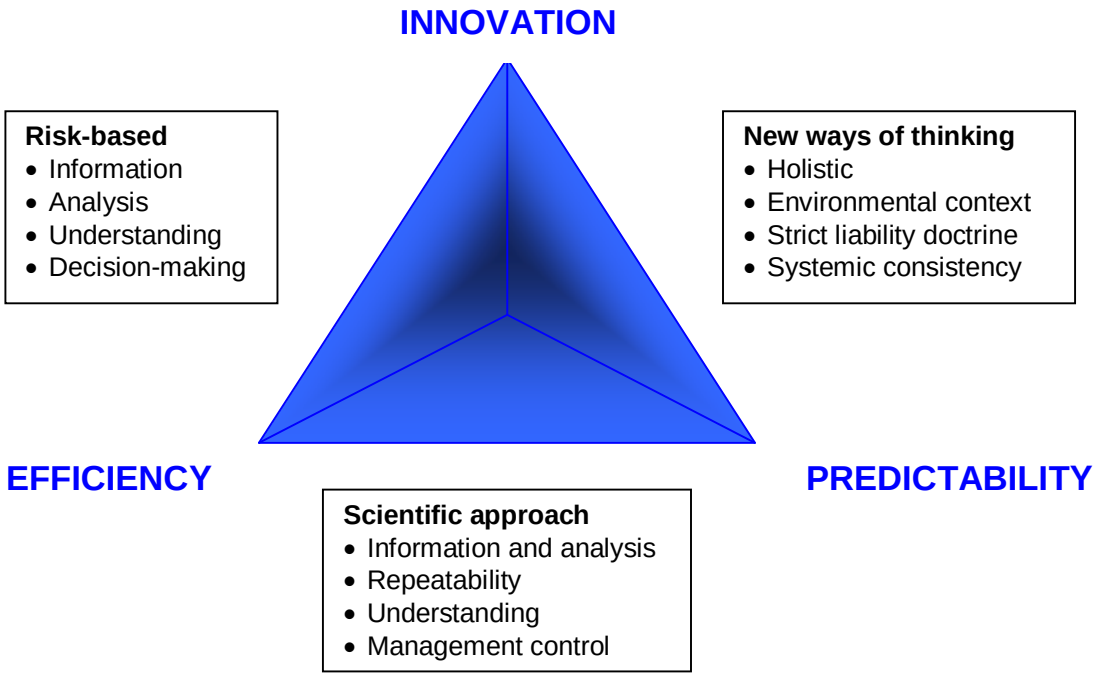


Figure 1 – FDA's three-fold challenge: to improve innovation, efficiency and predictability in drug development and manufacturing, *as per* [33].

The implementation of the product quality lifecycle management (PLM) is one of the new challenges for pharmaceutical companies. The PLM is a concept for managing product data throughout a drug's lifecycle from early development to extinction of the product. It is the basis to achieve the direct communication between the development team with the manufacturing department, in constant trade of new knowledge and updating the scientific fundamentals of the choices adopted for a given process. The PLM will provide an integrated framework for regulatory compliance, strategic sourcing, product specification and data management, manufacturing and corrective actions, product safety and quality control. Embracing these five objectives of a "value-driven compliance" approach promotes the reduction of costs and internal failures, anticipates revenue of invested capital, rewarding companies with reduced regulatory oversight and operational efficiency [33], while

companies that choose not to update their process management and join these efforts become at risk of not being able to follow the actual progress and survive to next years.

The implementation of QbD encloses three major components: knowledge capture, risk management and quality systems, that together will address to business benefits to the sponsor and the contractor and, most important, to patient. Once this strategy is working, a more accurate planning becomes possible, which will allow greater supply chain reliability and predictability, and that will drive down the cost of goods. A direct effect in product pricing and availability will be noted. On the other hand, effective knowledge management turn possible to the manufacturer to move towards innovative technologies enabling a proactive product lifecycle marketing plan in order to embrace new therapies and make them available sooner.

In terms of Production/QC planning, there will be no more validation's "rule of three". Typically, companies manufacture three batches at commercial scale before applying marketing approval of a new drug. If the analytical results of these three batches are in compliance with the specifications, it means the process works and can be considered validated. This concept comes from FDA's 1993 compliance policy guide on process validation. In March 2004, FDA revised the guide [38] and substituted the "three batches at commercial scale" reference with "adequate minimum proof of process validity", without any suggestion of a number. Other change introduced with this revision was the fact that those three batches are no longer validation batches, since process validation became a life cycle approach. FDA is also considering ways to improve manufacturers' flexibility and through the Pharmaceutical Quality Assessment System (PQAS) they expect to receive more information in new drugs applications about pharmaceutical development, manufacturing science, QbD and its implementation in unit operations, and especially on the scientific rationale behind a sponsor's proposals. With such approach FDA's hopes to grant companies a broader range to submit postapproval changes. The new system includes also a new quality overall summary (QOS) that will promote a carefully review of the critical aspects of companies' applications before submitting them, improving promptly the quality of the submissions and reducing time spent on revisions [38].

Process Analytical Technology

The PAT initiative in pharmaceuticals began in the 1990's. In 1993 there was an Association of Analytical Communities International Symposium entitled *Pharmaceutical Process Control and Quality Assessment by Non-Traditional Means*. Later in 2001, an Advisory Committee for Pharmaceutical Science (ACPS) meeting was held and discussed PAT. This meeting encouraged the formation of a PAT subcommittee within ACPS, which is formed by four working groups: 1) Benefits, technology, definitions/terminology, 2) Process and analytical validation, 3) Chemometrics, and 4) Product/process development. These working groups are composed of people from the FDA, industry, and academia [39].

Facing the actual economic crisis pharmaceutical companies are being forced to reduce spending. PAT implemented to manufacturing processes comes as a strategy to achieve this goal, as it consists in a methodology which directly measures an aspect of interest and quickly provides feedback on the quality of product or raw material.

PAT may be seen as a framework for innovative pharmaceutical development, manufacturing and quality assurance, and promises to modernize the way industry operates its product development. In a more scientific basis, PAT is accepted as a system for continuous analysis and control of manufacturing processes based on real-time measurements, or rapid measurements during processing, of quality and performance attributes of raw and in-process materials and processes to assure acceptable end product quality at the completion of the process [40]. This requires that multiple systems including process analytical chemistry tools, information management tools, feedback process control strategies are co-related, and strategies set-up for product/process design and optimization.

Creating consistent product quality means designing in quality at the earliest part of the product and process development phases of a new product. One of the key steps for implementing PAT is understanding how processes generate products from input materials and what influences unit operations have over critical product quality attributes. PAT is about measuring and understanding sources of variability through the process. Initially it may start by looking at raw materials used in the

formulation and then working through each unit operation until the final product. Once the process is understood from a scientific and engineering point of view, the risks to product quality can be identified, quantified and rated. This process understanding allows the identification of the high-risk process steps, and most important, to the identification of the critical control points [41].

A number of different technologies have been utilized to develop relationships between the physical chemical properties of drug product actives, excipients, or intermediates and final product performance. The most widely used on-line and at-line tool is Fourrier Transform - Near Infra Red (FT-NIR) spectroscopy, but there is also Raman spectroscopy, Fluorescence Spectroscopy, and for instance combined Nuclear Magnetic Resonance (NMR) with Fourrier Transformed - Infra Red (FT-IR) spectroscopy. The most important features about these techniques are the possibility of provide information on both chemical quality attributes and physical properties quickly, easily and without destroying the critical information. Its swiftness of giving outputs and operation mode makes them a fast way of creating a database of raw material information where can be confronted chemical, physical and batch-to-batch variance information, with rapid reimbursement to a company that invested on one of these techniques of monitoring processes. Some of the most common applications are testing packaging components, raw materials testing in the warehouse rather than the lab, at-line or on-line control of polymorphs, at-line or on-line blend uniformity testing, tracking drying processes, at-line or on-line tablet potency and content uniformity, measuring tablet coating thickness, online monitoring of clean-in-place efficiency (rather than cleaning and testing in the lab and then cleaning again if results are insufficient), and surface monitoring of equipment to verify cleaning. All of these different applications prompt a rapid response when issues arise and save time and money [39]. PAT used correctly can also reduce product development time, help improving understanding of critical in-process properties, aid in scale-up and technology transfers, and aid in troubleshooting.

After critical control points are identified, appropriate monitoring and control strategies can be applied. The placement of these along the process depends on the type of the product being manufactured, the degree of process knowledge in place at the time and the quality risk profile of the process. Measurement and control systems

can range from simple monitoring of raw material process feedstock through to integrated monitoring and active feed forward or feedback process control loops implemented within the manufacturing stages [41].

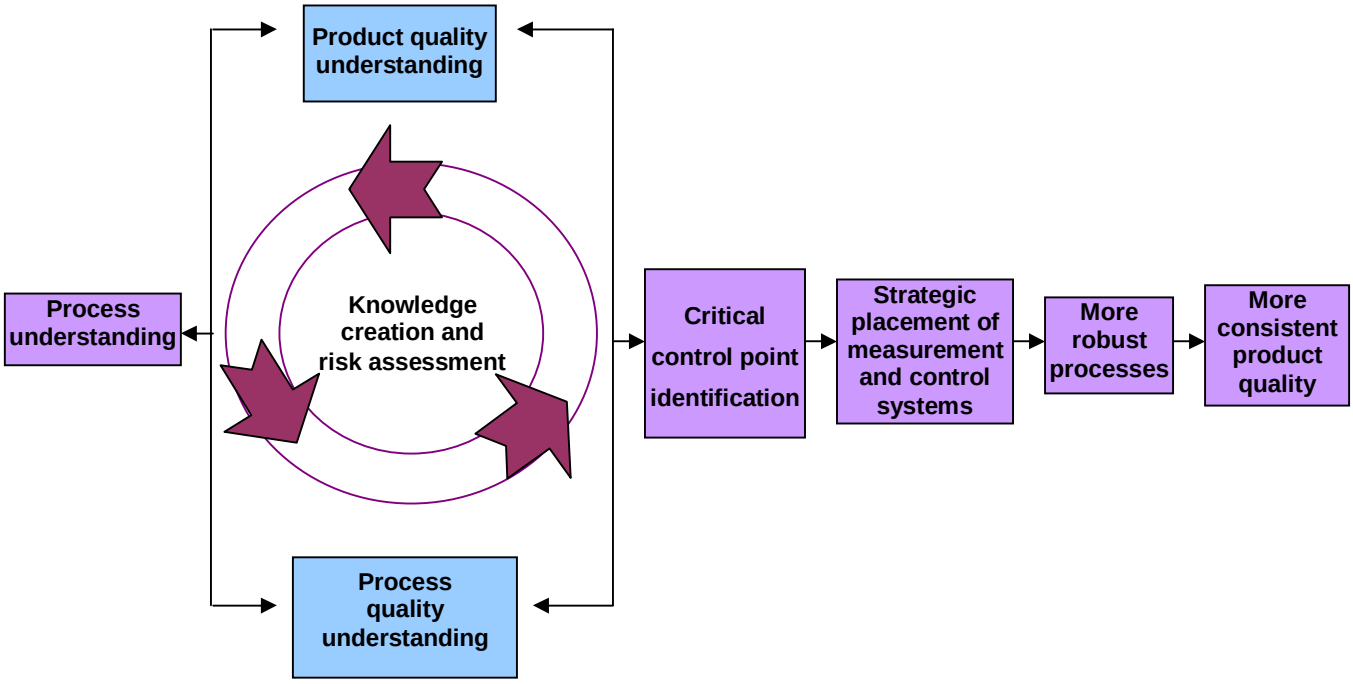


Figure 2 – PAT Process – Design for quality manufacturing, *as per* [41].

Monitoring systems can be in-line, on-line or at-line, depending on the criticality of the output information or the required speed of decision making necessary to react towards the process. The process knowledge and the risk assessments performed earlier in the process development will serve as base for this kind of decision. Figure 2 shows the way a PAT process shall be established in a design for quality manufacturing.

Using PAT to make decisions and adjust a manufacturing process doesn't require as much analytical expertise as does implementing PAT initially. Once PAT application is in routine use in a commercial manufacturing, process operators can make the approve/disapprove decisions on simplified graphic or alphanumeric output. Analytical experts are needed only for periodic revisions or troubleshooting, as long as standard maintenance procedures are followed [42].

The FDA recognizes industry hesitation to implement PAT and some regulatory uncertainty. Implementing PAT may include involving the FDA earlier in concurrent product development review. The FDA guidance *PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*, published in September 2004, has five sections: Introduction, Guidance Development Process and Scope, Background, PAT Framework (Process Understanding, Principles and Tools, Strategy for Implementation), and PAT Regulatory Approach. The goal of the guidance is to encourage voluntary development of innovative manufacturing and quality assurance approaches. FDA believes that PAT can be a "win-win" opportunity for both FDA and industry. The optimal application of modern analytical techniques in–process can reduce the rate of scrap/recalls, increase the efficiency of manufacturing and quality control, and provide a better scientific and engineering foundation for current FDA-industry debates [43].

From an industry point of view, new technology introduces new problems to face and industry is often struggling to meet the current regulatory expectations while maintaining a quick time to launch. Another concern is related to marketed products. There is a concern that adding PAT to older validated processes will uncover issues that are not visible with current quality control methods. On the other hand, PAT requires more effort up front to develop methods specific for the drug product being considered. There is also the additional complexity of the interpretation of data collected by PAT methods. While some methods are very straightforward, others collect a large amount of data and require sophisticated data analysis methodology to relate the output to an actual physical/chemical phenomenon. PAT can provide ways to recognize a finished product by the chemical or physical "fingerprint" that a process has to put on it, leading to tools and techniques that better identify counterfeit products. However, a "fingerprint" of the process is not very useful unless there is a good understanding of what the fingerprint is indicating. When there is a change in the fingerprint, it is necessary to know the significance of the change as it relates to product attributes and quality, and here comes the need for experts on the subject [42].

SPECIFIC STAGES AND ACTIVITIES OF PROCESS VALIDATION IN THE PRODUCT LIFECYCLE

The lifecycle approach emphasizes the importance of the product and process design in the development phase, the qualification of the commercial manufacturing equipment and process and the maintenance of the process in a state of control along routine commercial production [44].

A process validation should be viewed from now on as an ongoing acquisition of scientific knowledge and ongoing assurance. All the validation process strategy should be developed with an integrated team approach that includes expertise from a variety of disciplines, including process engineering, industrial pharmacy, analytical chemistry, microbiology, statistics, manufacturing, and quality assurance. Throughout the product lifecycle, various studies can be initiated to discover, observe, correlate, or confirm information about the product and process. A good project management and good archiving are essential to capture scientific knowledge gained along product development. These studies should be appropriately documented, and should be approved in accordance with the established procedure for the stage of the lifecycle.

The new guidance of FDA for validation processes in industry reflects some of the goals of FDA's initiative entitled *Pharmaceutical cGMP for the 21st Century – A Risk-Based Approach*, which consisted in the implementation of modern risk management and quality system tools and concepts, using technological advances in pharmaceutical manufacturing [35]. According to the 2008 FDA draft guidance, Process Validation is the collection and evaluation of data from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products. The three proposed stages for a process validation [1] are summarized in figure 3.

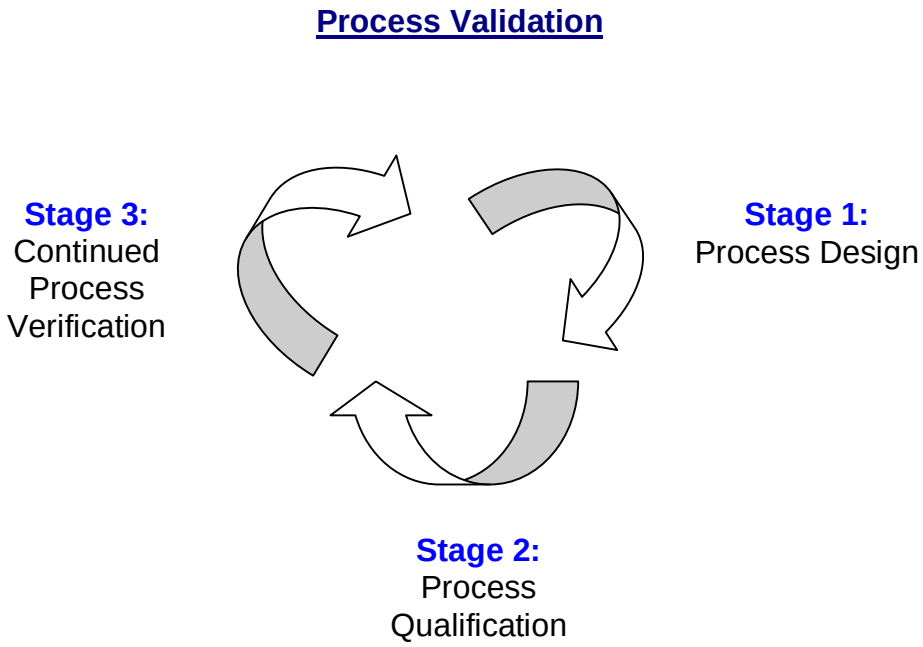


Figure 3 – Three stages Process Validation in product lifecycle, in continuous improvement, as proposed by the new guidance of FDA, *as per* [44].

Stage 1 – Process Design

This stage aims the development of methods and competencies for building and capturing process understanding and the use of such scientific knowledge as the basis for establishing an approach to effective process control in a routine commercial manufacturing.

Design of Experiment (DOE) studies can help develop process knowledge by revealing relationships, including multifactorial interactions, between the variable inputs and the resulting outputs. These tests shall be conducted in accordance with scientific methods and principles, including good documentation practices, as advised by the ICH guidance for industry Q10 *Pharmaceutical Quality System*. Here the risk analysis tools can be used to minimize the total number of tests required to DOE. The results provided from DOE studies should then elucidate about the ranges of incoming component quality, equipment parameters, and in process material quality attributes.

Manufacturers are expected to document all decisions and justification of the controls the variables studied for a unit operation and the rationale for those variables identified as significant in the lifecycle of the process and product. Documentation should reflect the basis for decisions made about the process. The Quality Control department should be asked to take part in this stage, like in routine commercial production. Product development activities provide key inputs to the design stage, such as the intended dosage form, the quality attributes, and a general manufacturing pathway. It is expected, in a regulatory sense, that the process is controlled within commercial manufacturing conditions, including all combinations of conditions posing a high risk of process failure.

Process knowledge and understanding is the basis for establishing an approach to process control for each unit operation and the process overall. Process controls address variability to assure quality of the product. Controls can consist of material analysis and equipment monitoring at significant processing points designed to assure that the operation remains on target and in control with respect to output quality. These controls are included in the master production and control records, as advised in 21 CFR 211.186(a) and (b) of the FDA cGMP regulations. A special emphasis is given to Process Analytical Technology (PAT) and its recent advances, in real time analysis, with an easier control loops to adjust the processing conditions so that the process output remains constant and reproducible. In case of choosing PAT as a control strategy, the approach to process qualification will focus on the qualification of the measurement system and control loop [1, 44].

cGMP documents for commercial manufacturing are key outputs of Stage 1. Companies should have a diagram of the process flow for the full-scale process.

Stage 2 – Process Qualification

In this stage of a validation process, the process design is confirmed as being capable of reproducible commercial manufacture, through two tasks: Design of a facility and qualification of utilities and equipment, and Performance Qualification.

a) Design of the Facility and Qualification of Utilities and Equipment

In this item, the guidance refers the two prerequisites to achieve pharmaceutical quality: a proper facility design and a project attitude in the start-up of a facility. Moreover, there is a definition for “qualification” as the activities undertaken to demonstrate that utilities and pieces of equipment are fitting their intended use and perform properly. The guidance indicates a list of activities the qualification of utilities and equipments should include, taking into account that operating ranges should be shown capable of being held as long as would be necessary during routine production.

The plan can incorporate quality risk management, aligned with ICH Q9 guidance, to prioritize certain activities and to identify a level of effort in both the performance and documentation of qualification activities. The plan should state the studies or tests to use, the criteria appropriate to assess outcomes, the timing of qualification activities, responsibilities, and the procedures for documenting and approving the qualification.

At the end of this stage, there must be a well organized report with all the qualification activities documented and summarized, with conclusions that address criteria in the plan, which must be reviewed and approved by the quality control unit, according to the 21 CFR 211.22 of CGMP regulations [1,44].

b) Performance Qualification Approach

The Performance Qualification (PQ) combines the actual facility, utilities, equipment (already qualified in the previous stage), and the trained personnel with the commercial manufacturing process, control procedures, and components to produce commercial batches.

A successful PQ will confirm the process design and demonstrate that the commercial manufacturing process performs as expected. The decision to begin commercial distribution should be supported by data from commercial batches,

although data from laboratory and pilot studies can provide additional assurance. The cumulative data from all relevant studies (e.g., designed experiments; laboratory, pilot, and commercial batches) should be used to establish the manufacturing conditions in the PQ. Employment of objective measures (e.g., statistical metrics) is strongly recommended, wherever feasible and meaningful to achieve adequate assurance [1].

The 1987 FDA guidance described Process Performance Qualification as being a process oriented to equipment and processes performance for clean utilities, cleaning and sterilization processes. This was different from Product Performance Qualification, more oriented to the commercial manufacturing performance. According to this new FDA guidance, these two parts of Process and Product Performance Qualification tend to be combined within this stage in order to achieve an overall goal of Performance Qualification. Success at this stage is consider meaningful for product lifecycle and must be completed before a manufacturer starts commercial distribution of the pharmaceutical product [44].

In this stage of process validation, it is essential to create a written protocol that specifies the manufacturing conditions, controls, testing, and expected outcomes. That protocol must ensure that the manufacturing conditions set for the PQ were thought based on the cumulative data from all relevant studies, as DOE's, laboratory, pilot and commercial batches. The way measures are made to evaluate the outputs, for instance, chemometrics or statistics, are important to demonstrate that adequate assurance has been achieved. During PQ, an improved level of monitoring, sampling and testing should confirm a uniform product quality throughout the batch during processing. This attitude should also continue initially into the continued process verification stage.

From now on there is no three rule batches for process validation, since there is no fixed number for PQ batches prescribed, but manufacturers will have to justify their rationale used when deciding how many batches are necessary to assure the whole PQ. There is only the suggestion of more than one batch, since the expression used in the guidance is always as "commercial batches", in plural. According to the guidance, PQ batches should be manufactured under normal operating conditions respecting to utility systems (e.g., air handling and water purification), material,

personnel, environment, and manufacturing procedures. This means extremes of operating conditions are not expected for this stage of process validation [44]. The commercial manufacturing process and routine procedures must be followed, according to sections 211.100(b) and 211.110(a) of the cGMP regulations [12].

For PQ protocol, FDA guidance provides some recommendations on its format and content, as well as for the final report [1]:

PQ Protocol	***PQ Report***
➢ Manufacturing conditions, including operating parameters, processing limits, and raw material inputs; ➢ Data to be collected and respective plan of evaluation; ➢ In-process, release and characterization tests to be performed and acceptance criteria for each significant processing step; ➢ Sampling plan (statistically meaningful) and frequency of sampling for each unit operation and attribute. Risk analysis can help to define a level of confidence; ➢ Design and qualification of facilities, utilities and equipment, personnel training and qualification, and verification of material ➢ Status of the validation of analytical methods used in measuring the process, in process materials, and the product sources;	❖ A discussion and cross-reference all aspects of the protocol; ❖ A summary of data collected and analysis of the data, as specified by the protocol; ❖ An evaluation of any unexpected observations; ❖ A summary and discussion all manufacturing non-conformances such as deviations, aberrant test results, or other information that has bearing on the validity of process; ❖ A description of any corrective actions or changes that should be made to existing procedures and controls; ❖ A clear conclusion as to whether the data indicates the process met the conditions established in the protocol and whether the process is considered to be in a sufficient state of control;

PQ Protocol	*PQ Report*
➢ Provision for dealing with deviations from expected conditions and decisions upon nonconforming data; ➢ Review and approval by appropriate departments and the quality unit.	❖ Documented justification for the approval of the process, and release of lots produced by it to the market, based on all knowledge and information gained from the design stage through the process qualification stage; ❖ All appropriate department and quality unit review and approvals.

During the stage 2, cGMP-compliant procedures must be followed and successful completion of this stage is necessary before commercial distribution. Products manufactured during this stage, if acceptable, can be released, but FDA expects that concurrent release will be used rarely [1]. Concurrent release might be appropriate for processes of limited demand as for orphan drugs, or processes with low production volume per batch like with radiopharmaceuticals. When warranted and used, concurrent release should have a cautious supervision of the distributed batch to allow that customer complaints and defect reports should be rapidly assessed to determine root cause and whether the process should be improved or changed. Each batch in a concurrent release program must also undergo stability testing and its data must be evaluated on time to guarantee rapid detection and correction of any problems.

Stage 3 – Continued Process Verification

The goal of this stage is to continually assure that the process remains in a state of control (the validated state) during commercial manufacture [1]. Adherence to the cGMP requirements, specifically including the collection and evaluation of information and data about the performance of the process, will allow detection of

process drift. Robust systems have to be implemented for detecting unplanned drift from the designed process [44]. The evaluation should determine whether action must be taken to prevent the process from drifting out of control (section 211.180(e)) [13].

The data collected should include relevant process trends and quality of incoming materials or components, in-process material, and finished products. The data should be statistically trended and reviewed by trained personnel. It is recommended to perform a statistical study from the data collected, to make an evaluation of process capability and stability. All this data shall be organized to constitute a Data Collection Plan in order to demonstrate that the Critical Quality Attributes (CQAs) are being controlled along the process.

FDA recommends that the manufacturer use quantitative, statistical methods whenever feasible, as well as intra-batch and inter-batch variation as part of a comprehensive continued process verification program and also to evaluate process stability and capability. Variation can also be detected by the timely assessment of defect complaints, out-of-specification findings, process deviation reports, process yield variations, batch records, incoming raw material records, and adverse event reports. Production line operators and quality unit staff shall be encouraged to provide feedback on process performance, and the quality unit is expected to meet periodically with production staff to evaluate data, discuss possible trends or drifts in the process, and coordinate any correction or follow-up actions by production. Maintenance of the facility, utilities and equipment is another important aspect of ensuring that a process remains in control [1, 44].

It is expected that from this observations and brainstorming, come out new ideas and ways to improve and/or optimize the process by altering some aspect of the process or product such as the operating conditions (ranges and set-points), process controls, component, or in-process material characteristics. All these changes must be well-justified, and lead according an implementation plan, and quality unit approval before implementation must be documented (21 CFR 211.100) [12]. These modifications may warrant performing additional process design and process qualification activities. Once established, qualification status must be maintained through routine monitoring, maintenance, and calibration procedures and

schedules for facilities, utilities, and equipment (21 CFR part 211, subparts C and D) [11] must be planned.

As far as documentation is concerned, the degree and type of records required by cGMP is greater during Stage 2 and Stage 3. Studies during these stages must conform to cGMP and must be approved by the quality unit in accordance with the regulations (21 CFR 211.22 and 211.100) [1,11].

PQLI CRITICALITY, DESIGN SPACE AND CONTROL STRATEGY

By applying risk assessment and experimental design ISPE PQLI initiative has as its main goal facilitating the implementation of ICH Q8, ICH Q9 and ICH Q10 guidance. QbD, which is a concept introduced by ICH Q8 for pharmaceutical development, consists in a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding based on solid scientific principles and quality risk management [32]. The increased process knowledge and product understanding, achieved through QbD, can be translated into significant business benefits. For example, QbD can induce to a lower cost of quality, since it enables science-based understanding of processes and permit to manufacturers concentrate their control efforts on those factors that are critical to quality. A greater process understanding also means more robust processes that can accommodate the most likely variations in raw materials that occur over time. On the other hand, having confidence in the ability to maintain operations' specification within the limits, companies can free resources for more productive investment, reduce manufacturing costs, improve yield, increase equipment uptime, plant and capacity utilization, reduce rework and fewer rejected batches, product recalls and compliance actions. In case of being a research and development dedicated company, by maximizing the probability that a product in development will make through scale-up, technology transfer and validation, QbD will contribute to reduction of the time to market and speed up return on investment. Another asset of QbD lies on the reduction of regulatory burden, since the manufacturing processes within the design space can be continuously improved without further regulatory review. In a more general way, all departments, from quality control and analytical laboratories to process development to manufacturing and regulatory submission and compliance, every human resources in a company will have to work together having the design space in mind as the framework for their common efforts [45].

From an engineering point of view, QbD can promote the use of new technologies and the use of new approaches to perform process validation, such as continuous quality verification.

The first step to develop a systematic knowledge inventory is determining what information will be most useful to submission of a product, to release a product, to manufacture a product, the potential of a facility, the capacity required along the product lifecycle, what will be needed to control the product and what will be required to manage post-approval submissions. Next, a manufacturer should determine what of these aspects are already determined and what will have to be explored. All this survey and resulting knowledge are necessary to understand what is critical to the product and works as a foundation for understanding the facility requirements. After this stage, a design space must be developed wherein will be possible to make the pretended product successfully, in terms of process environment and facilities. Finally, the knowledge and the conditions determined to promote the quality of final product will stand the creation of a control strategy that will support the consistence of the process and robustness of its results, by application of engineering solutions to equipment, to materials and to facilities, all necessary to maintain the process within the design space [36]. The relation between these components of Quality by Design is represented in Figure 4:

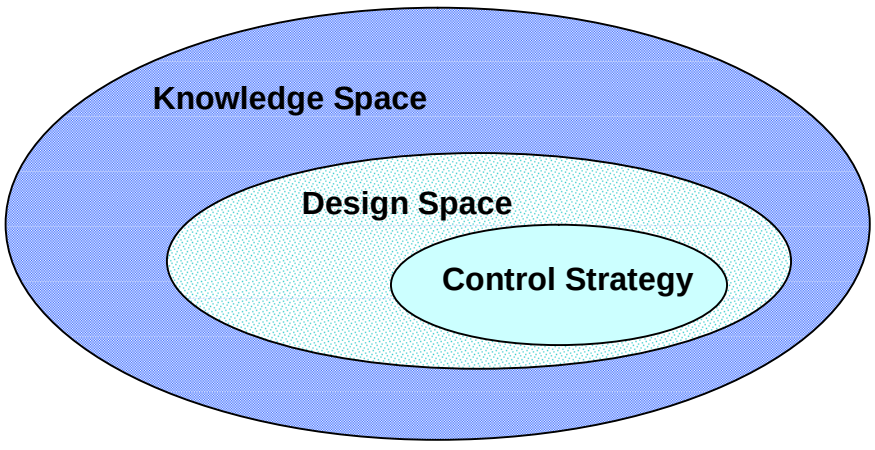


Figure 4: Quality by Design Interdependencies, *as per* [36].

For the implementation of Quality by Design philosophy, there are three topics considered fundamental: criticality, design space and control strategy [32]. These topics are explained below.

Criticality

Criticality consists in any feature or material attribute, property or characteristic of a drug substance, component, raw material, drug product or device, or any process attribute, parameter, condition or factor in the manufacture of a drug product. The assignment of attributes or parameters as critical or non-critical is an important outcome of the development process that provides the foundation for deciding what is or isn't included in the Design Space. The designation of criticality should be made relative to the impact that quality attributes or process parameters have on the safety, efficacy and quality of the product. With increased process knowledge and understanding, quality attributes and process parameters can undergo multiple iterations to reclassify their categorization, as necessary. Therefore, this is not a static assessment.

Risk assessments should consider cause and effect relationships, relative to probability, severity, and sensitivity. Probability is the likelihood of harm occurring, while severity is the measure of the possible consequence. Sensitivity refers to the ability to discover or determine the existence, presence, or fact of a hazard, and also the attenuation of interactions between multivariate dimensions. Risk management is central to the exposition of criticality and includes risk identification, risk evaluation, risk control, and risk communication, as proposed in ICH Q9 [46].

The main question here is "What is the potential for variables to impact quality?" The answer is likely to distinguish the category of criticality, by separating variables that do not have an impact on quality, designated as non-critical, from the critical ones [46]. Several levels of criticality may be used to describe multiple levels of risk. As the boundaries for a quality attribute or parameter approach edges of failure, the level of criticality increases with the level of risk.

As process understanding and knowledge increase during the lifecycle of a product the delineation of criticality serves as an interactive process to re-evaluate the risk of process variables and quality attributes.

A process is considered well understood from physico-chemical perspective when the sources of variability are explained, quality attributes can be predicted based on key inputs, like process parameters, material attributes, and finally, when process capability of quality attributes meets acceptance levels.

Design Space

According to ICH Q8 [28], Design Space is the multi-dimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.

The American Society for Testing and Materials (ASTM) defined design space as the multi-dimensional region which encompasses the various combinations of product design, manufacturing process design, manufacturing process operating parameters and raw materials quality which product material of suitable quality [36].

A Design Space well performed together with an appropriate Control Strategy will reduce end product testing, increasing process performance and robustness. ICH Q9 provides an excellent framework for Quality Risk Management, including risk assessment. It also refers different tools that can be used to make that assessment, like Hazard Analysis and Critical Control Points (HACCP), “Worst Outcomes Analysis”, Failure Mode Effects and Criticality Analysis (FMECA) [47].

Like criticality, Design Space continuous to evolve as additional knowledge and information is generated during the commercialization of the product. According to ICH Q8, “working within the design space is not generally considered a change of the approved ranges for process parameters and formulation attributes” [28]. This guidance also includes a regulatory aspect, when states that if parameters become out of the approved design space, then there is a change and a regulatory post-approval change process should be initiate. This can be subject to reflection case by case and discussed with the respective health authorities, but one solution that has been adopted is to overlay the business requirements on the design space and then use risk management for the product to decide a strategy that will best consent a rational degree of flexibility within the defined area [36].

To elaborate a Design Space, one must start by defining the Pharmaceutical Target Product Profile (PTPP), which identifies the desired performance characteristics of the product. Prior knowledge and a preliminary risk assessment can help to determine experiments to be performed for the initial investigation about the importance of quality attributes and process parameters, including the quality of raw materials, and packaging components. Multivariate models based on chemistry, biotechnology, or engineering fundamentals can be used to build the Design Space [47]. Any process parameter is critical since it has a direct or indirect impact on patient safety, therapeutic efficacy, in vivo pharmacokinetic or pharmacodinamic performance, or product manufacturing [36]. The goal of the experimentation and modelling is to create an understanding of all variables that impact CQAs, which are quantifiable properties of the intermediate or final product that are critical to reach the product's intended quality, efficacy and safety. Then, there must be a linkage in the form of a Design Space [47].

The Design Space is linked to criticality through the results of risk assessment, which determines the associated CQAs and Critical Process Parameters (CPPs). The CPPs are process inputs that have a direct and significant influence on the CQA, and for that reason must be kept within a limit range. This is the kind of information that keeps increasing along the lifecycle of a product and should be recorded and well organized [36].

The Design Space describes the multivariate functional relationships between CQAs and the CPPs that impact them, and should include their linkage to or across unit operations. These relationships are revealed through joint application of risk assessment and experimental design, modelling, as well as the use of literature and prior experience.

The Design Space also contains the proven acceptable ranges (PAR) for CPPs and acceptable values for their associated CQAs. Normal operating ranges are a subset of the Design Space and are managed under the company's Pharmaceutical Quality System (PQS) [32].

Control Strategy

Risk assessment is fundamental to determining critical processes extent and development of the design space. Risks should be determined on cause and effect and relative to probability of a consequence, as well as the severity or magnitude of the impact of a consequence. It is also necessary to know at what level a consequence can be measured, as well as sensitivity or attenuation of interactions between the various dimensions. The important here is to control process risks to the degree that they might exceed the limits of the design space [36]. The results of the risk assessment identify those CQAs and CPPs that are included in the Design Space and subsequently must be included in the control strategy.

In ICH Q10 [30], control strategy is defined as:

"a planned set of controls derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in process controls, finished product specifications and the associated methods and frequency of monitoring and control."

The control strategy may include, for example, raw material purchase specifications, API characteristics, operating ranges for process parameters, in-process controls and their corresponding acceptance criteria, release testing, and API or drug product specifications and their acceptance criteria [32].

The ISPE PQLI Control Strategy Team has proposed a Control Strategy Model [48] that seeks to link the attributes of the product that are important to the patient, to the controls in the manufacturing process that are needed to deliver those attributes, and also to show in parallel the business requirements. The Control Strategy should link from pharmaceutical drug development through manufacturing including process engineering equipment control. This model logic is intended to facilitate the regulatory discussion and is represented in figure 5.

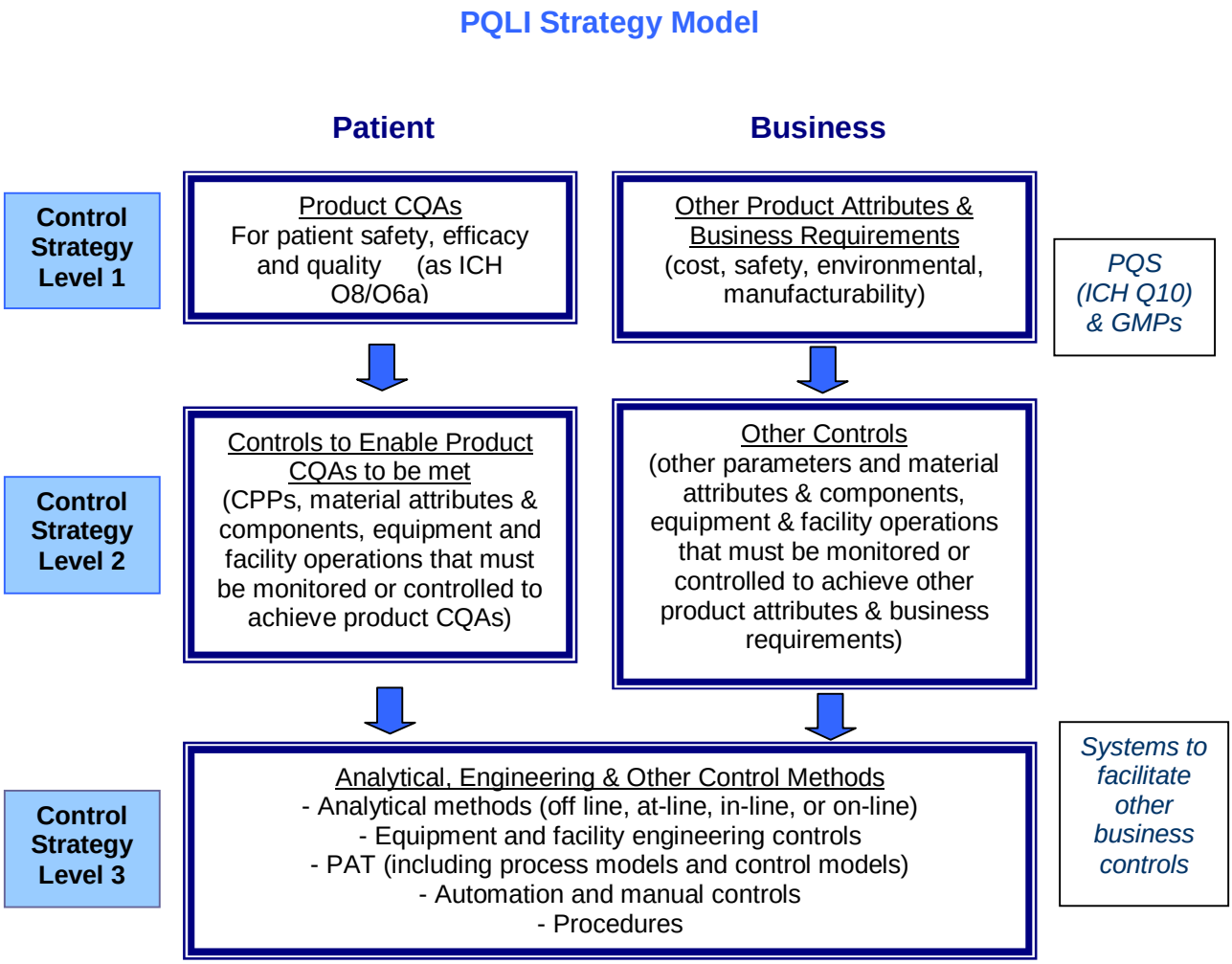


Figure 5 – The PQLI control strategy model, *as per* [48]

This model contains three levels from the finished product CQAs and other objectives through the manufacturing operations to the controls by which these are achieved and, two columns that distinguish between patient and business requirements.

At Control Strategy Level 1 the CQAs of the product are identified. Those product quality attributes that directly relate to patient safety, efficacy and quality are derived from the PTPP using prior knowledge, clinical experience, product and process understanding. Business requirements may include cost, efficiency, operator safety, environmental protection, manufacturability, other customer needs, and

supply related objectives. For an oral solid product, Drug Substance attributes considered may include appearance, identity, polymorphism, crystal habit, assay, surface energy, impurities, solvents, water content, particle size, sulphonated ash, and metals. For Drug Product the attributes normally considered important are friability, identification, appearance, dissolution, assay, content uniformity, degradation, purity, microbiology, and packaging [48].

The Control Strategy Level 2 considers the attributes of the starting materials, reagents, and solvents that must be monitored or controlled, and what parameters and operating conditions of the process equipment and manufacturing facility need to be monitored or controlled to ensure the objectives defined at Control Strategy Level 1 are achieved [48].

At Control Strategy Level 3 the analytical and other controls methods are included, as well as the measurement technologies for the material attributes or equipment parameters (off-line, at-line, in-line or on-line), univariate or multivariate process models and control models, as well as procedural and engineering controls of the plant including automation systems, closed control loops, normal operating ranges, and alarms. This Level should also describe the multivariate process models to be used, including what these process models will do, and how they will be operated and maintained. This process model should be maintained within the company's own PQS [48].

Finally, as showed in Figure 5, the control strategy is implemented within a framework comprising the PQS and GMPs for the patient-related product attributes, and other aspects such as Environmental, Health and Safety systems, and financial systems for the business-related requirements [48].

PROPOSAL FOR A PHARMACEUTICAL PROCESS REVALIDATION

1. INTRODUCTION

The following work in this thesis consisted of studying an industrial process of an existing commercialized product, composed of a mixture of 4 active substances formulated in capsules.

Currently the manufacturing process consists of raw materials sieving followed by a blending stage, where all the active substances and excipients are mixed. The filling operation is performed in an intermittent motion capsule filler with a low output, and manual feeding by the operator. This process was validated in 2005 [51], and since then more than one hundred batches were produced successfully. However, this industrial production process presents a batch to batch content uniformity variability of some of their active substances in finished product analysis. This problem was observed occasionally in some batches, but the results of the analysis of finished product did not show a clear relationship with neither an earlier stage of the process, nor any raw material physical characteristic that could have lead to the observed variability.

The main goal of this thesis is to propose a new approach for process revalidation integrated with the lifecycle of this pharmaceutical product. This means that this new approach will take into account principles from ICH 8, ICH Q9 and ICH Q10 guidance. This will be achieved through integration of knowledge and background data from Manufacturing, Quality Control, Quality Assurance and Process Development areas, which are used to work in a segmented way. Since this is a process of an existing commercialized product, the following work will propose an approach for planning a process optimization with minimal changes and consequent process revalidation. The objective is to perform blend's gravimetric discharge, instead of manual feeding, to the encapsulation machine, without increasing the variability observed in the current process. With the gravimetric discharge option, the filling operation would be performed with a high-speed capsule filler, with clear advantages for the process in terms of yield/time ratio.

Next, the chapter 2 of this thesis will present the current process flowchart. In chapter 3 of this thesis, the process background data will be reviewed, including conclusions taken from process validation performed in 2005 [51], an extended evaluation of product analytical data report (2005) [52] and a product characterization report (2006) [53]. In chapter 4 of this thesis, there is a risk assessment (FMECA) to evaluate the most critical parameters in this process and what actions are required to minimized the occurrence of failures. Finally in chapter 5, an experimental design will be proposed taking into account the conclusions from the previous risk assessment, focusing on 3 aspects:

a) The physical characterization of active substances;

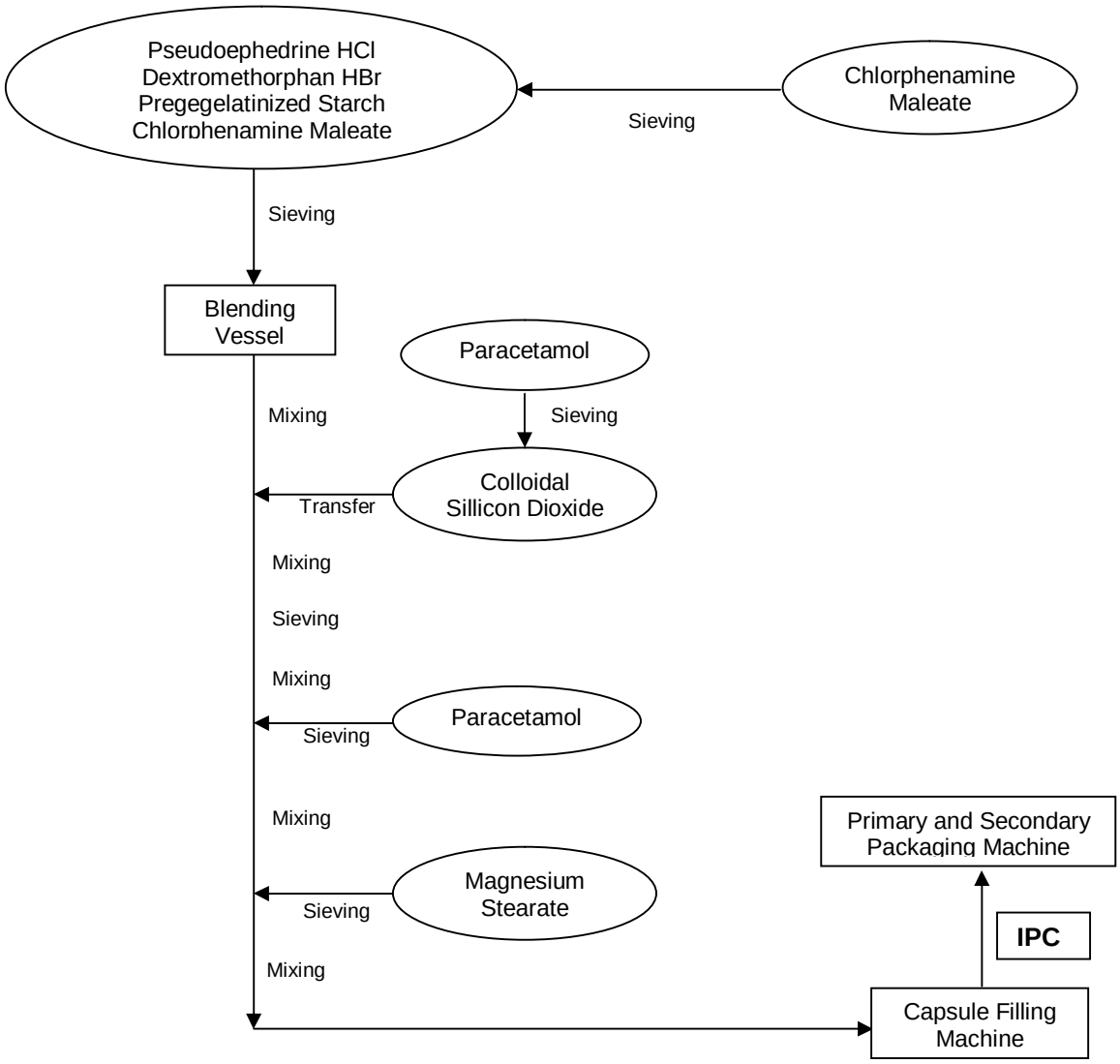
b) The identification of the critical parameters of the gravimetric discharge system;

c) The design of experiments where the critical parameters of the active substances and the gravimetric discharge system are tested together.

2. PRODUCTION PROTOCOL

This formulation is composed of four active substances: paracetamol, dextrometorphan bromidrate, chlorphenamine maleate and pseudoephedrine hydrochloride. The following excipients are used: pregelatinized starch, as diluent, magnesium stearate as lubricant, and colloidal silicon dioxide as an anti-binder. This formulation has components with very different particle sizes and densities, which can represent a problem when the process consists of a simple mixture of all the components, followed by gravity discharge to the hopper of the encapsulation machine.

Process Flowchart



IPC includes tests to in bulk product such as capsules' aspect, individual and average fill weight, closed capsules size, disintegration, dissolution of paracetamol, content uniformity of pseudoephedrine HCl, Dextromethorfan HBr and chlorphenamine maleate, single dose uniformity of paracetamol, assay of the 4 active substances, degradation compounds and microbiological purity.

All these tests have their own acceptance criteria, previously established during the galenic development of this product and have also been registered in the Common Technical Document for this product.

3. PROCESS BACKGROUND DATA

3.1. Process Validation 2005

This manufacturing process was validated in 2005 [51]. The process validation protocol required the verification of homogeneity of the final blend in 10 points of the blending vessel (top, centre and bottom) as figure 6, before discharge to the capsule filler.

Sampling points:
1-Left upper side
2-Centre upper side
3-Right upper side
4-Left middle side
5-Centre middle side
6-Right middle side
7-Left bottom side
8-Centre bottom side
9-Right bottom side
10-Discharge

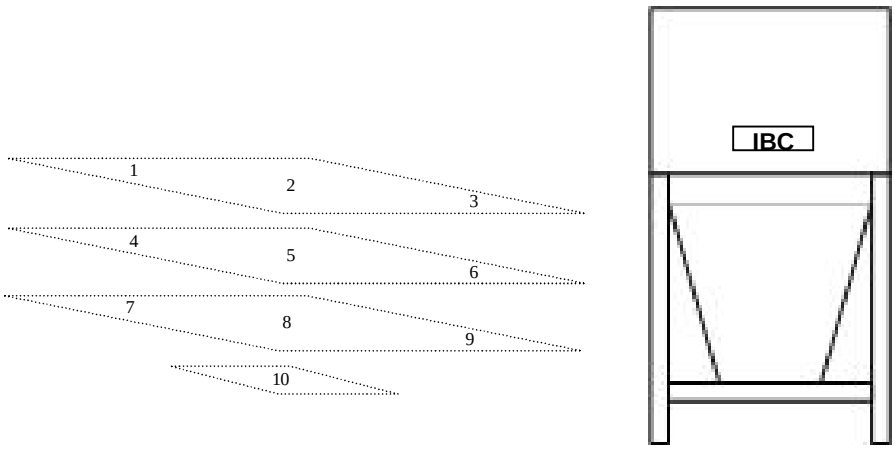


Figure 6- Sampling plan for content homogeneity verification.

In the 3 consecutive validation batches, all content uniformity results of the 4 active substances were within specifications. Ideally, the discharge of the mixture from the intermediate bulk container (IBC) should be done through a discharge station connected to a pipe to the hopper of the machine (Figure 7).

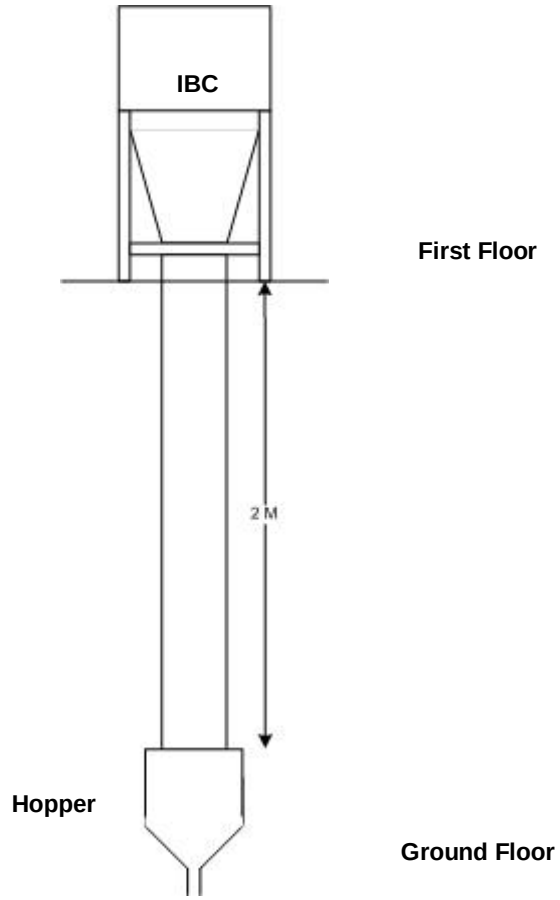


Figure 7 - Representation of elements present in a gravity discharge situation: Blend's IBC in the first floor, discharge pipe, hopper of encapsulation machine in the ground floor.

In order to evaluate the future possibility of gravimetric discharge of the mixture, avoiding the existing manual feeding process, additional tests were performed in one of the 3 validation batches, to evaluate the impact of gravimetric discharge in content uniformity results:

a) 10 Kg of mixture was gravimetric discharged and filled;

b) 10 kg of mixture was manually feeded into the machine hopper by the operator;

In the first trial a), the content uniformity for Pseudoephedrine HCl showed 1 result OOS (out of 10) and a RSD of 8,4%. The acceptance limits for content

uniformity is 85-115% and 6% for the RSD. The other 3 active substances content uniformity results were within specifications.

The second trail b) showed all API's content uniformity within specifications and with a lower RSD.

These results gave an indication that segregation could occur during the gravity discharge process.

As a result of these trials, the possible application of the gravimetric discharge to the product was abandoned.

3.2. Extended analytical analysis 2003-2005

In 2005 a statistical analysis of analytical results for the assay and content uniformity observed in batches produced between 2003 and 2005 was performed [52]. In this study there was a tendency for more scattered values of content uniformity and Chlorphenamine Maleate and Pseudoephedrine HCl assays, when compared to values observed for Paracetamol or Dextromethorfan HBr.

3.3. Characterization Report 2006

In 2006 new trial batches were performed [53] to evaluate possible gravimetric discharge, this time using special stainless steel devices, inserts, inside the discharge tube, to slow down the mixture falling speed, and minimize blend segregation. The gravimetric discharge exposes the blending to a fall from a height of about 2 m. Three different trial experiments were performed, in order to study the best option to minimize the variability of capsules content uniformity which was already observed with the manual discharge process.

1) Gravimetric discharge with an insert, as shown in figure 8 followed by filling by a high-speed capsule filler;

2) Manual discharge and filling by high-speed capsule filler;

3) Gravimetric discharge with a modified insert with more paddles inside the discharge tube, as shown in figure 9, to slow down the product transfer, and filling by high-speed capsule filler;

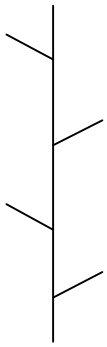


Figure 8 - Insert 1

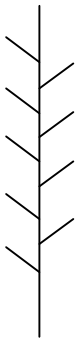


Figure 9 - Insert 2

The content uniformity was evaluated in each trial in 3 capsules from the beginning, 3 capsules from the middle and 4 capsules from the end of the filling process.

Trial 1 Results: Content uniformity results comply within the acceptance criteria with exception of the results for Dextromethorfan HBr which had one individual value and relative standard deviation (RSD) out of specification. For Dextromethorfan HBr and Pseudoephedrine an increase of the content at the end of the filling process was also observed. Mass uniformity was always observed to be within specifications.

Trial 2 Results: Content uniformity results for the 4 active substances comply with the acceptance criteria, with low RSD values, showing homogeneous content throughout the filling process. Mass uniformity results within specifications.

Trial 3 Results: Content uniformity results shown low RSD values for the 3 active substances tested (Dextromethorfan HBr, Pseudoephedrine HCl and Chlorphenamine Maleate) throughout the filling process, without any tendency to increase or decrease from the beginning to the end. Mass uniformity results within specifications.

Conclusions:

These trials permit to conclude that it is possible to obtain product complying with Ph Eur mass uniformity and content uniformity specifications when using a gravimetric discharge and a high-speed capsule filler (trial 3). However the results observed also demonstrated that slowing down the final blend fall is a critical parameter in order to maintain its homogeneity and avoid blend's segregation. This homogeneous flow was achieved using an insert with paddles as shown in Figure 9 (trial 3). Nevertheless the process was not modified.

3.4. Historical Batch Data Review 2008

In the following tables there is a review of the results observed in batches produced in 2008 [54], 8 out of 54 batches manufactured in this year. In these selected batches, the content uniformity variability for Pseudoephedrine HCl and Chlorphenamine Maleate throughout the filling process is more critical. These are batches where the Pseudoephedrine HCl content uniformity had a RSD value higher than 4%.

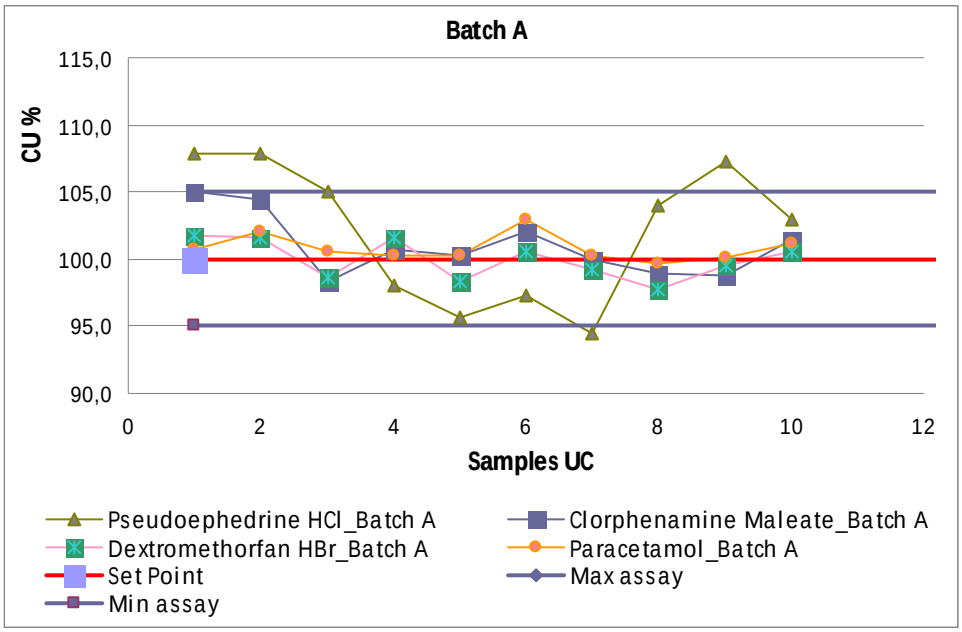
Next to each table there is the respective graph which represents the variability of content uniformity along the process for each active substance, depending on whether the samples were taken at the beginning or at the end of the filling process. In 10 capsules tested, 3 are from the beginning of filling process, 4 from the middle and the last 3 from the end of filling process. Those graphics have horizontal lines for 95% and 105%, because every time the content uniformity stands outside the 95%-105% limit (assay limits), there is a tendency for assay results be close to the upper limit.

Batch A

Assay (%)			
Pseudoephedrine HCl	**Chlorphenamine Maleate**	**Dextromethorfan HBr**	**Paracetamol**
102,0	100,1	99,7	101,2

Content Uniformity (%)				
Samples	**Pseudoephedrine HCl (%)**	**Clorphenamine Maleate (%)**	**Dextromethorfan Br (%)**	**Paracetamol (%)**
1	107,8	105,0	101,8	100,7
2	107,9	104,4	101,6	102,0
3	105,0	98,4	98,6	100,5
4	98,1	100,7	101,6	100,3
5	95,6	100,2	98,3	100,3
6	97,3	102,1	100,6	102,9
7	94,5	100,0	99,2	100,3
8	104,0	98,9	97,7	99,6
9	107,3	98,8	99,5	100,1
10	102,9	101,4	100,5	101,2
Average (%)	102,0	101,0	99,9	100,8
Std Dev	5,2	2,3	1,5	1,0
RSD (%)	5,1	2,3	1,5	1,0

Table 2 – Assay and Content Uniformity for batch A



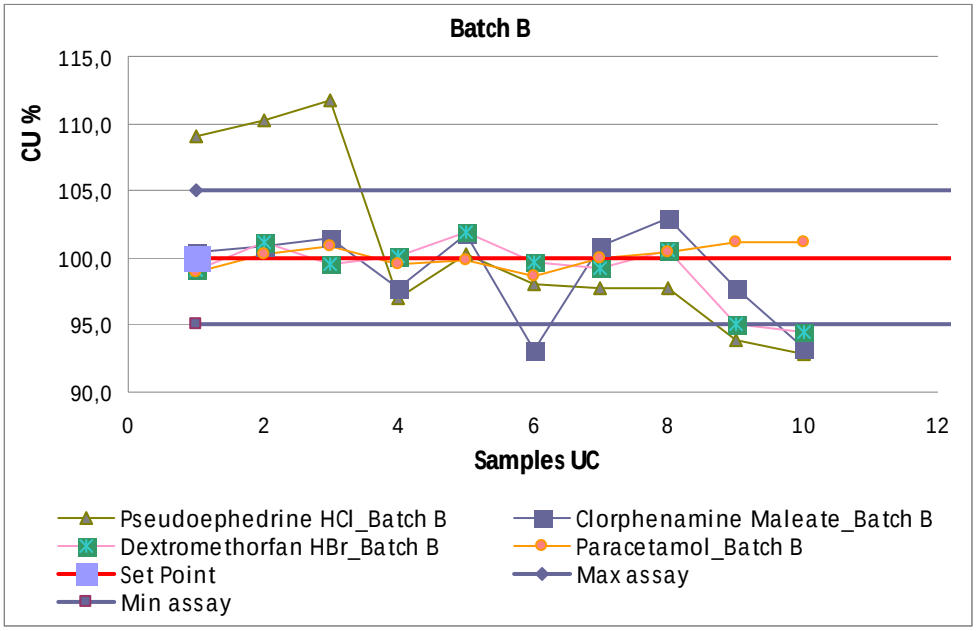
Graph 1 – SPC for active substances content uniformity of batch A

Batch B

Assay (%)			
Pseudoephedrine HCl	**Chlorphenamine Maleate**	**Dextromethorfan HBr**	**Paracetamol**
100,7	97,6	99,9	99,6

Content Uniformity (%)				
Samples	**Pseudoephedrine HCl (%)**	**Clorphenamine Maleate (%)**	**Dextromethorfan Br (%)**	**Paracetamol (%)**
1	109,0	100,4	99,1	98,9
2	110,3	100,9	101,1	100,2
3	111,8	101,4	99,5	100,8
4	97,0	97,7	100,1	99,5
5	100,3	101,8	101,9	99,8
6	98,1	93,1	99,6	98,6
7	97,8	100,9	99,3	100,0
8	97,8	102,9	100,5	100,4
9	93,8	97,7	95,1	101,2
10	92,8	93,3	94,4	101,1
Average (%)	100,9	99,0	99,1	100,1
Std Dev	6,9	3,5	2,4	0,9
RSD (%)	6,9	3,5	2,5	0,9

Table 3 – Assay and Content Uniformity for batch B



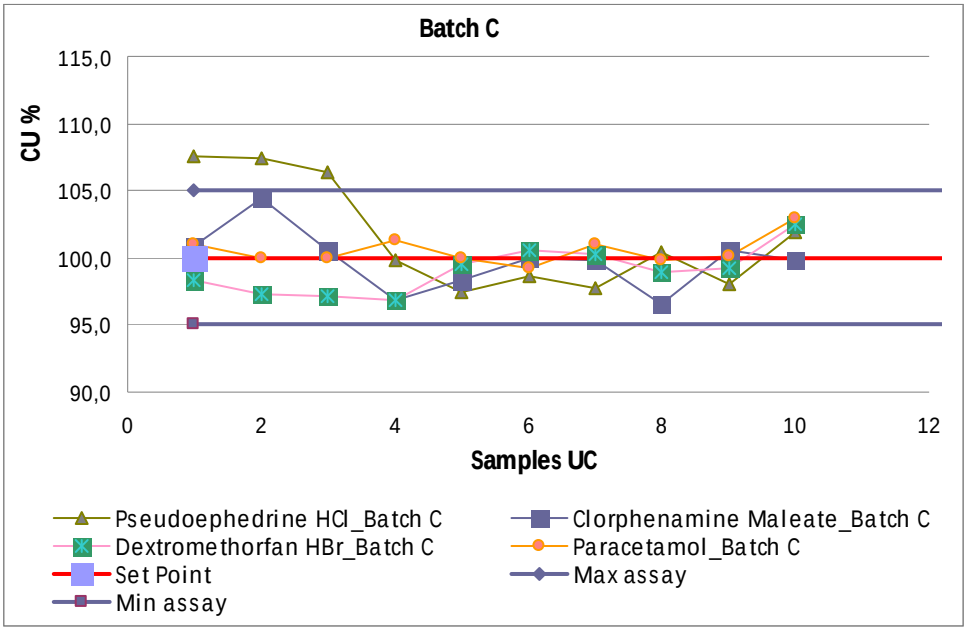
Graph 2 – SPC for active substances content uniformity of batch B

Batch C

Assay (%)			
Pseudoephedrine HCl	**Chlorphenamine Maleate**	**Dextromethorfan HBr**	**Paracetamol**
99,9	97,6	99,2	101,1

Content Uniformity (%)				
Samples	**Pseudoephedrine HCl (%)**	**Clorphenamine Maleate (%)**	**Dextromethorfan Br (%)**	**Paracetamol (%)**
1	107,6	100,8	98,4	101,0
2	107,4	104,4	97,3	100,0
3	106,4	100,6	97,2	100,0
4	99,8	96,9	96,9	101,3
5	97,4	98,3	99,5	100,0
6	98,6	100,0	100,6	99,3
7	97,7	99,8	100,2	101,0
8	100,4	96,5	98,9	99,8
9	98,0	100,5	99,3	100,1
10	101,9	99,8	102,5	103,0
Average (%)	101,5	99,8	99,1	100,6
Std Dev	4,1	2,2	1,7	1,1
RSD (%)	4,1	2,2	1,8	1,1

Table 4 – Assay and Content Uniformity for batch C



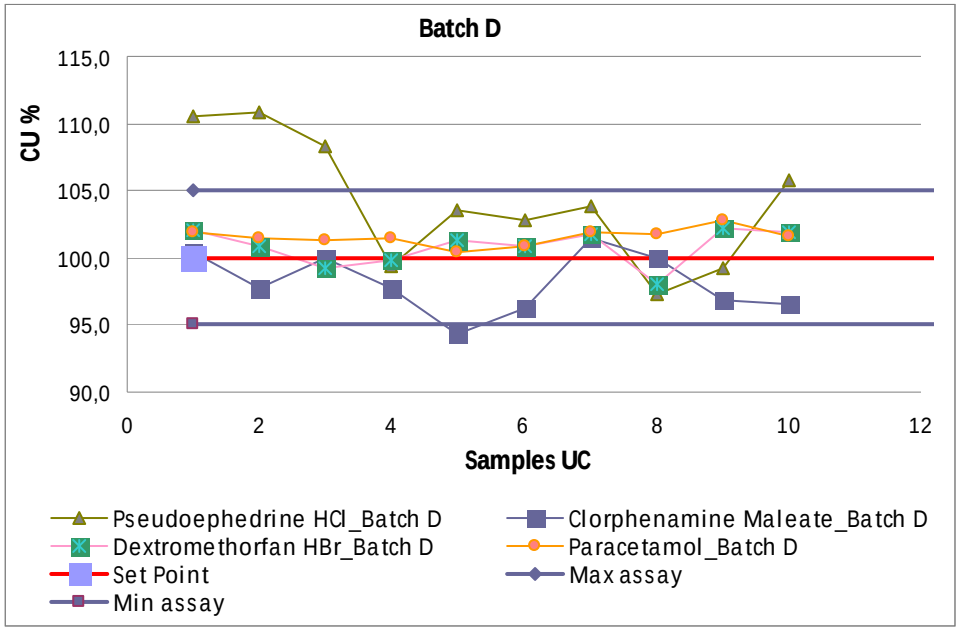
Graph 3 – SPC for active substances content uniformity of batch C

Batch D

Assay (%)			
Pseudoephedrine HCl	**Chlorphenamine Maleate**	**Dextromethorfan HBr**	**Paracetamol**
103,5	96,3	100,2	101,1

Content Uniformity (%)				
Samples	**Pseudoephedrine HCl (%)**	**Clorphenamine Maleate (%)**	**Dextromethorfan Br (%)**	**Paracetamol (%)**
1	110,5	100,4	102,0	101,9
2	110,9	97,7	100,9	101,4
3	108,3	100,0	99,2	101,3
4	99,4	97,8	99,8	101,4
5	103,5	94,3	101,3	100,4
6	102,8	96,3	100,8	100,9
7	103,8	101,4	101,8	101,9
8	97,3	99,9	98,1	101,8
9	99,2	96,9	102,2	102,8
10	105,7	96,5	101,9	101,6
Average (%)	104,1	98,1	100,8	101,5
Std Dev	4,7	2,2	1,4	0,6
RSD (%)	4,5	2,3	1,4	0,6

Table 5 – Assay and Content Uniformity for batch D



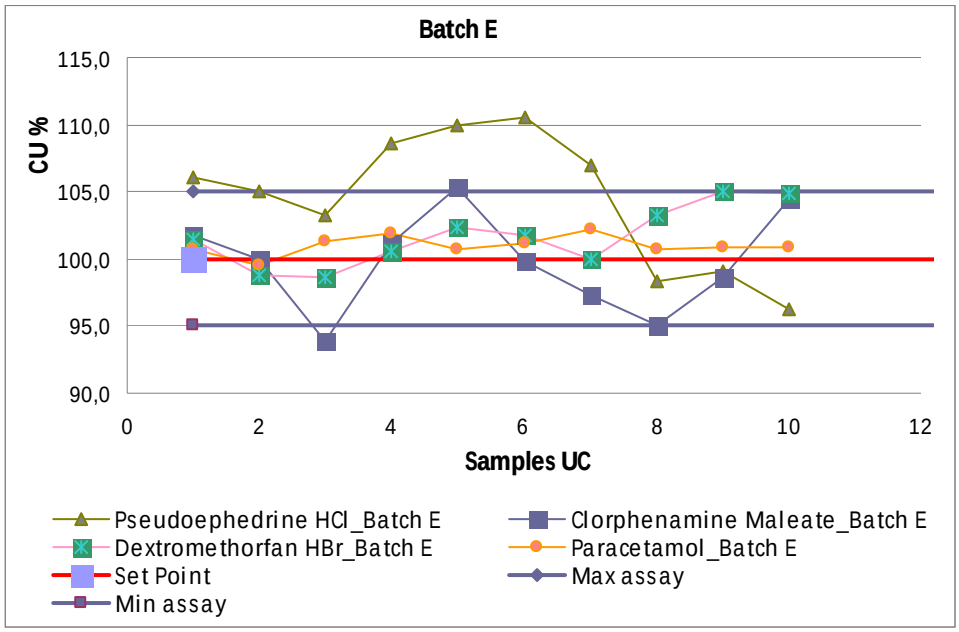
Graph 4 – SPC for active substances content uniformity of batch D

Batch E

Assay (%)			
Pseudoephedrine HCl	**Chlorphenamine Maleate**	**Dextromethorfan HBr**	**Paracetamol**
103,9	98,1	98,5	101

Content Uniformity (%)				
Samples	**Pseudoephedrine HCl (%)**	**Clorphenamine Maleate (%)**	**Dextromethorfan Br (%)**	**Paracetamol (%)**
1	106,1	101,8	101,5	100,7
2	105,1	100,0	98,8	99,5
3	103,2	93,9	98,7	101,3
4	108,6	101,2	100,6	101,9
5	109,9	105,4	102,4	100,7
6	110,5	99,8	101,8	101,2
7	106,9	97,3	99,9	102,2
8	98,4	95,0	103,3	100,7
9	99,1	98,7	105,0	100,8
10	96,2	104,5	104,9	100,8
Average (%)	104,4	99,8	101,7	101,0
Std Dev	5,0	3,7	2,3	0,7
RSD (%)	4,8	3,7	2,2	0,7

Table 6 – Assay and Content Uniformity for batch E



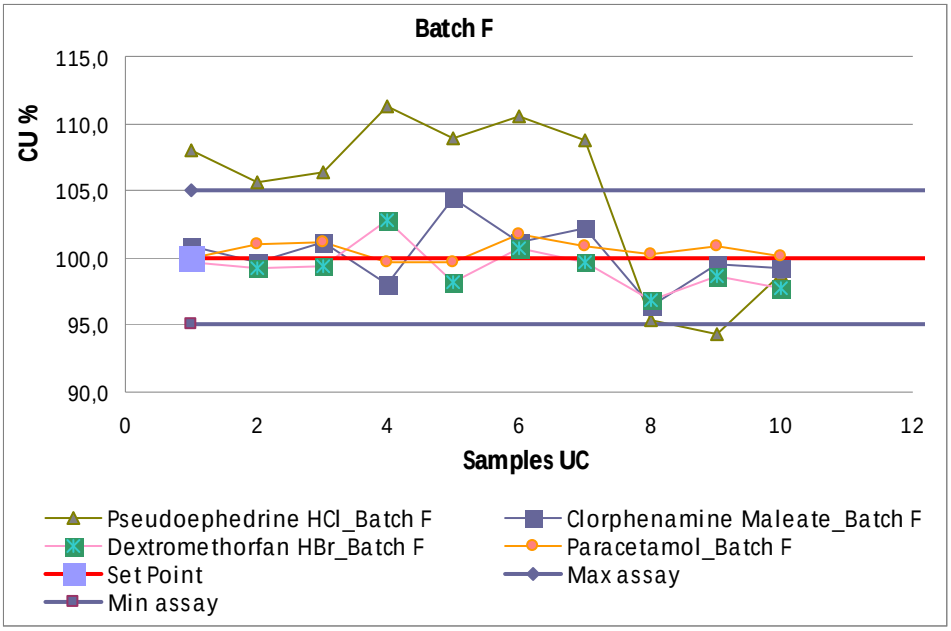
Graph 5 – SPC for active substances content uniformity of batch E

Batch F

Assay (%)			
Pseudoephedrine HCl	**Chlorphenamine Maleate**	**Dextromethorfan HBr**	**Paracetamol**
104,7	100,0	101,6	100,9

Content Uniformity (%)				
Samples	**Pseudoephedrine HCl (%)**	**Clorphenamine Maleate (%)**	**Dextromethorfan Br (%)**	**Paracetamol (%)**
1	108,0	100,8	99,7	99,9
2	105,6	99,6	99,3	101,0
3	106,4	101,2	99,4	101,1
4	111,3	98,1	102,8	99,6
5	108,9	104,5	98,2	99,6
6	110,5	101,1	100,7	101,8
7	108,7	102,2	99,6	100,8
8	95,4	96,4	96,8	100,3
9	94,3	99,5	98,7	100,8
10	98,8	99,3	97,7	100,1
Average (%)	104,8	100,3	99,3	100,5
Std Dev	6,3	2,2	1,7	0,7
RSD (%)	6,0	2,2	1,7	0,7

Table 7 – Assay and Content Uniformity for batch F



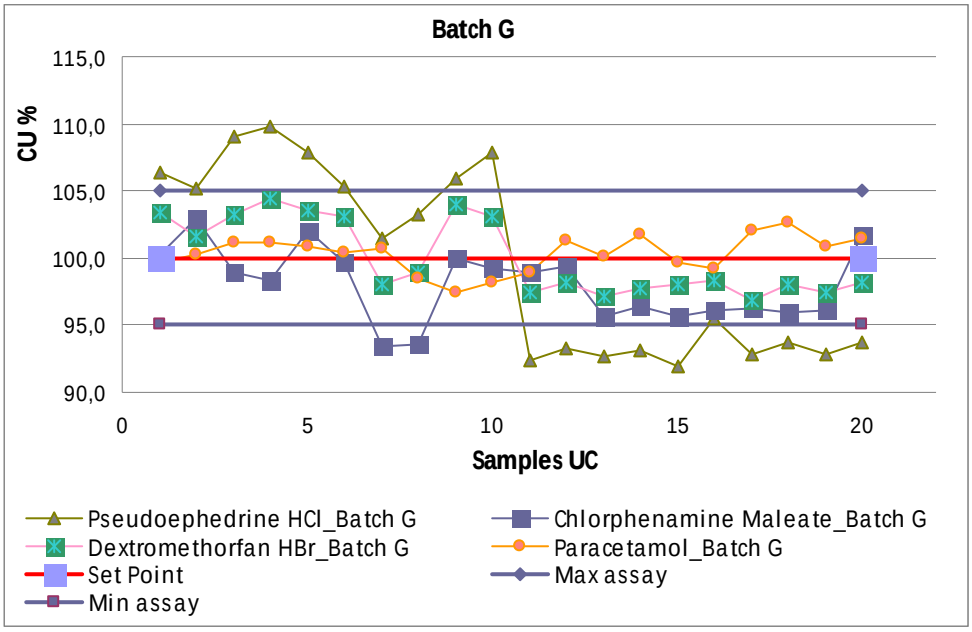
Graph 6 – SPC for active substances content uniformity of batch F

Batch G

Assay (%)							
Pseudoephedrine HCl		**Chlorphenamine Maleate**		**Dextromethorfan HBr**		**Paracetamol**	
Inicio	Fim	Inicio	Fim	Inicio	Fim	Inicio	Fim
106,4	92,3	101,6	96,3	102,9	96,8	*	*

Content Uniformity (%)								
	Pseudoephedrine HCl		**Chlorphenamine Maleate**		**Dextromethorfan HBr**		**Paracetamol**	
	Inicio	Fim	Inicio	Fim	Inicio	Fim	Inicio	Fim
1	106,4	92,4	100,3	99,0	103,4	97,4	99,7	98,9
2	105,2	93,2	102,9	99,4	101,6	98,3	100,2	101,3
3	109,1	92,7	98,9	95,7	103,2	97,1	101,1	100,1
4	109,8	93,1	98,3	96,4	104,5	97,7	101,1	101,8
5	107,8	91,9	102,1	95,6	103,5	98,1	100,9	99,7
6	105,4	95,5	99,6	96,1	103,1	98,3	100,4	99,2
7	101,5	92,8	93,4	96,2	98,1	96,8	100,7	102,0
8	103,2	93,7	93,6	96,0	99,0	98,0	98,5	102,6
9	105,9	92,8	99,9	96,1	104,0	97,5	97,5	100,9
10	107,8	93,7	99,3	101,7	103,1	98,2	98,2	101,4
Average	106,2	93,2	98,8	97,2	102,3	97,7	98,8	100,8
Std Dev	2,6	1,0	3,1	2,1	2,2	0,5	1,3	1,3
RSD (%)	2,4	1,1	3,2	2,1	2,1	0,5	1,3	1,2

Table 8 – Assay and Content Uniformity Results for Batch G



Graph 7 – SPC for active substances content uniformity of batch G

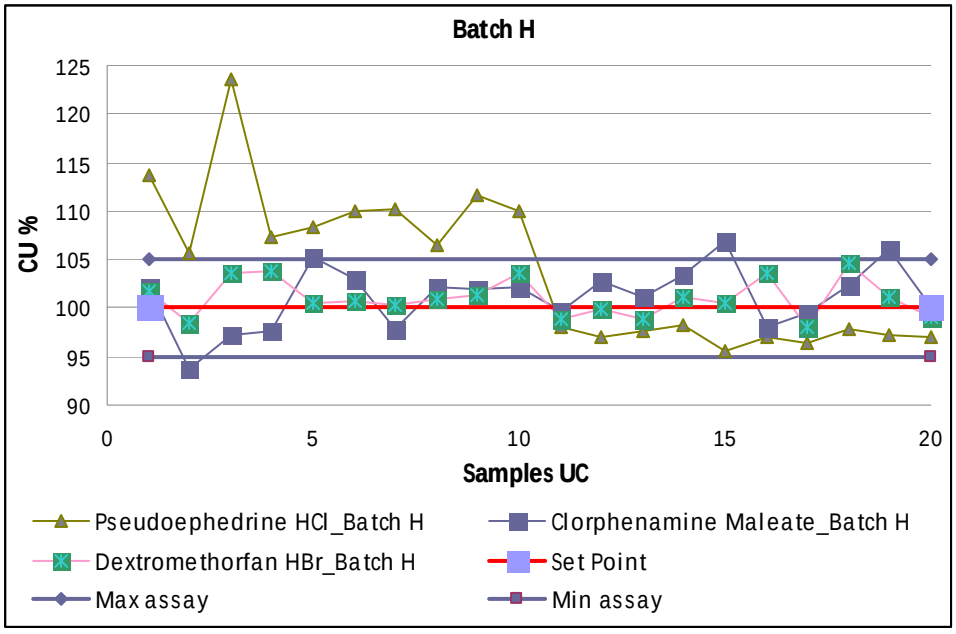
Batch H

Assay (%)							
Pseudoephedrine HCl		**Chlorphenamine Maleate**		**Dextromethorfan HBr**		**Paracetamol**	
Inicio	Fim	Inicio	Fim	Inicio	Fim	Inicio	Fim
110,0	95,4	101,3	100,0	101,6	100,7	*	*

Content Uniformity (%)								
	Pseudoephedrine HCl		**Chlorphenamine Maleate**		**Dextromethorfan HBr**		**Paracetamol**	
	Inicio	Fim	Inicio	Fim	Inicio	Fim	Inicio	Fim
1	113,6	98,0	102,2	99,6	101,8	98,9	*	*
2	105,7	96,9	93,8	102,8	98,5	99,9	*	*
3	123,6	97,7	97,3	101,1	103,6	98,9	*	*
4	107,2	98,3	97,6	103,3	103,7	101,1	*	*
5	108,3	95,5	105,2	106,9	100,5	100,5	*	*
6	109,9	96,9	103,0	98,0	100,7	103,6	*	*
7	110,2	96,3	97,8	99,4	100,3	98,1	*	*
8	106,5	97,8	102,1	102,4	100,9	104,7	*	*
9	111,6	97,3	102,0	106,0	101,3	101,2	*	*
10	110,0	97,1	102,1	100,0	103,6	99,1	*	*
Average	110,7	97,2	100,3	101,9	101,5	100,6	*	*
Std Dev	5,1	0,9	3,5	2,9	1,7	2,1	*	*
RSD (%)	4,6	0,9	3,5	2,8	1,7	2,1	*	*

** Values not available*

Table 9 – Assay and Content Uniformity Results for Batch H



Graph 8 – SPC for active substances content uniformity of batch H

CONCLUSIONS FROM BACKGROUND DATA:

1) Process Validation 2005: When the mixture was manually feeded into the machine hopper by the operator, all API's content uniformity were within specifications and with a lower RSD than when a gravity discharge was performed. These results gave an indication that segregation could occur during the gravity discharge process, so the possible application of the gravimetric discharge to the product was abandoned.

2) Trial batches 2006: The gravimetric discharge was tested in experimental trials (part 3.3.). The results showed that the blending flow should be constant and slow, and this was achieved with the insert of more paddles (Figure 9). The results from this trial demonstrated that it was possible to obtain product complying with Ph Eur mass uniformity and content uniformity specifications when using a gravimetric discharge.

3) Historical data 2008: The problem of content uniformity of the active substances was observed occasionally in some batches with a manual discharge process (part 3.4.). According to Table 2 up to Table 9, segregation of active substances seems to occur throughout the encapsulation process, since samples from the beginning of filling process have different content uniformity values from those in samples from the end of filling process.

4. RISK ASSESSMENT

Having in mind conclusions taken from process background data, a risk assessment must be made, in order to enhance the critical parameters inherent to each stage of the bulk manufacturing process under consideration. Guidance ICH Q9 gives some suggestions of useful tools for risk assessment analysis. In this case, the Failure Modes Effects and Criticality Analysis (FMECA) was the chosen risk assessment tool, because the critical parameters can be identified through it and it become possible to evaluate the severity of the consequences of eventual failures. The objective of FMECA is to identify the elements of systems most likely to cause failure, so that these potential failures can then be minimized or eliminated from the process.

When doing the FMECA risk assessment, it was necessary to analyze the way this process operates, and identify for each of the possible failure mode:

a) the effect on performance of failure

b) the probability of failure

c) the severity of failure

Then a value to each of these factors was assigned. Failure modes were then prioritized as a function of their severity (**S**), probability of occurrence (**O**) and detectability (**D**). Based on this prioritization, action should be taken afterwards to prevent failure or minimized the possibility of failure occurring.

The severity (**S**) factor describes the degree of reduced functionality/compliance resulting from the failure. This can be scored on a scale from 1 to 10, with a high score implying seriously reduced functionality, and a low score representing little or no effect.

The occurrence factor (**O**) of a particular mode of failure can be fixed also on a scale from 1 to 10, with a higher number being scored for more probable failures.

The detectability (**D**) factor describes the likelihood of the failure not being detected by the design process before the product is already at the market. It can be

scored from a 1 to 10 scale, where a score of 1 indicates that the failure will be found every time, and a score of 10 indicates that the failure will not be detected before the product is in the market.

In Annex 1 there are 3 tables with a detailed description of the scaling of each factor **S**, **O** and **D**.

A criticality index or risk priority number (RPN) was calculated according to the following formula:

$$\mathbf{RPN = S * O * D}$$

The higher the resulting RPN, the more urgent the need to find a solution.

This FMECA was made in a top-down approach, also named “system-level” approach, often used to reduce the amount of analysis that must be carried out [55]. This type of FMECA was chosen, instead of a bottom-up approach, because the aim of this study is to suggest an approach for planning a optimization of this process. Since this is a process which involves many parameters with many interactions between them along the process, it would be useful to do a pre-selection of the most critical process stages or a pre-selection of the parameters along the process which are more crucial to the final quality of the product. This system-level FMECA started by identifying the functional blocks containing high risk parameters and these blocks were then analyzed in more detail.

The packaging stage of process was not considered in this risk assessment because the object of study of this thesis is only the bulk process, not the finished product manufacturing process.

Failure Modes Effects and Criticality Analysis (FMECA)

Process: Product X Bulk Manufacturing

Purpose: Detection of process critical parameters

Process Stage	Parameter	Failure Mode	Potential Failure Cause(s)	Failure Effect	Actual Situation					Action Required
					Control Strategy	Severity	Occurrence	Detection	RPN	
Mixing	Content Homogeneity	Results of content homogeneity out of specification for each API (spec. 90-110%)	-Not enough mixing time -Different particle size distribution between components -Different density between components	-Non homogeneous distribution of components in the bin -No compliance with finished product required quality	Content homogeneity test (HPLC) for samples taken from the top, middle and bottom of the mixture bin (total of 10 samples)	9	2	3	60	No action required since all analysis performed showed results within specifications.
	Loss on Drying (LOD)	Results of LOD out of specification (spec. ≤1,5%)	-Moisture in bin's atmosphere -Inefficient moisture control in room's atmosphere and inside the equipment used for mixture	-Powder mixture with clusters -Powder flowability compromised	LOD test performed at the end of blending, with samples taken from the top, middle and bottom of the bin (total of 3 samples)	7	1	3	21	This parameter is only analysed as internal guidance and it is not a registered specification. No action required since all analysis performed showed results within specifications.

Failure Modes Effects and Criticality Analysis (FMECA) *(continuation of previous page)*										
Process Stage	**Parameter**	**Failure Mode**	**Potential Failure Cause(s)**	**Failure Effect**	**Actual Situation**					**Action Required**
					Control Strategy	**Severity**	**Occurrence**	**Detection**	**RPN**	
Mixing	Particle Size	Results of Particle Size out of specification (specs.: NMT 10% > 500μm NMT 25% > 250μm NMT 40% < 90 μm	-Incorrect choice of raw materials -Wide range of particle size distribution between API's and excipients -Inefficient individual sieving test -Use of sieves with net's pores damaged or not calibrated	-Problems in content homogeneity -Problems in discharge process (maintaining content homogeneity) -Different flow rate than expected -Problems in capsules filling (uniformity of mass) -Segregation problems enhanced	Particle size test performed in samples taken from the top, middle and bottom of IBC (total of 3 samples)	7	2	5	70	No action required since all analysis performed showed results within specifications.
	Density	Results of loose bulk and/or tapped density out of specification specs.: Loose Bulk (0,667-0,909g/ml) Tapped density (0,714-1,000g/ml)	-Incorrect choice of raw materials -Inefficient raw materials' previous quality control	-Problems in mixing efficiency -Problems in discharge process (maintaining blend's content homogeneity) -Segregation problems	Density tests performed in samples taken from the top, middle and bottom of IBC (total of 3 samples)	7	2	4	56	No action required since all analysis performed showed results within specifications.

Failure Modes Effects and Criticality Analysis (FMECA) *(continuation of previous page)*

Process Stage	Parameter	Failure Mode	Potential Failure Cause(s)	Failure Effect	Actual Situation					Action Required
					Control Strategy	Severity	Occurrence	Detection	RPN	
Mixing	Flow Rate	Results of Flow Rate out of specification (spec: < 60 seg/100g)	-Moisture in powder mixture -Particle size distribution out-of-specification (OOS) -Mixture density OOS -Tendency for clustering and cohesion effects between particles	-Problems in filling process (filling speed) -Problems in content homogeneity (not efficient mixing)	Flow rate test performed in samples taken from the top, middle and bottom of IBC (total of 3 samples)	6	2	2	24	No action required since all analysis performed showed results within specifications.
	Angle of Repose	Results of angle of repose out of specification (specs.: <40º)	-Moisture in powder mixture -Particle size distribution out-of-specification (OOS) -Mixture density OOS -Tendency for agglomeration and cohesion effects between particles (flowability problems)	-Problems in filling process (filling speed) -Problems in discharge process (maintaining blend's content homogeneity)	Angle of repose test performed in samples taken from the top, middle and bottom of IBC (total of 3 samples)	6	2	2	24	No action required since all analysis performed showed results within specifications.

Remark about Mixing Stage:
All these tests mentioned in control strategy were only performed for process validation activities. Since all results were in compliance with specifications previously established, this stage of the manufacturing process is considered validated and under control. In other words, there is no evidence of any problem related with mixing stage, so the process improvement proposals in this thesis will not be focused in the mixing stage.

Failure Modes Effects and Criticality Analysis (FMECA) *(continuation of previous page)*

Process Stage	Parameter	Failure Mode	Potential Failure Cause(s)	Failure Effect	Actual Situation					Action Required	Remarks
					Control Strategy	Severity	Occurrence	Detection	RPN		
Encapsulation	Assay of each API	Result OOS (spec. 95% – 105%)	-Lack of blend's content homogeneity after discharge -Powder mixture segregation	-Quality of finished product compromised -Non compliance with registered specifications	-Process Validation: HPLC assay of each API performed on samples taken from the beginning, middle and end of filling process (total of 3x10 capsules) -Routine test: HPLC assay of each API performed on a sample composed of capsules taken from the beginning, middle and end of filling process (total of 20 capsules)	10	3	2	60	-Decrease possibility of segregation -Decrease content homogeneity problems after powder discharge -Detect mechanical parameters critical in discharge component to avoid segregation along the falling	-Study of raw materials individually and their CQA's -Study critical components in powder discharge (having in mind that gravimetric discharge will promote the decrease of blend's content homogeneity during the filling process)

Failure Modes Effects and Criticality Analysis (FMECA) *(continuation of previous page)*

Process Stage	Parameter	Failure Mode	Potential Failure Cause(s)	Failure Effect	Actual Situation					Action Required	Remarks
					Control Strategy	Severity	Occurrence	Detection	RPN		
Encapsulation	Content Uniformity of each API	Result OOS (spec. 85% – 115%)	-Lack of blend's content homogeneity after discharge - Powder mixture segregation -Individual weight variability	-Variability of individual content of each API variable according the capsule is from the beginning, the middle or from the end of filling process -Quality of finished product compromised -Non compliance with registered specifications	-Process Validation: content uniformity test for each API performed on samples taken along the filling process (HPLC for all API's, except for Paracetamol which is performed through UV-visible) (total of 4 capsules x10 samples along the process) -Routine test: content uniformity test for each API performed on samples taken from the beginning, the middle and the end of the filling process (HPLC for all API's, except for Paracetamol which is performed through UV-visible) (total of 10 capsules)	10	4	3	120	-Decrease possibility of segregation -Decrease content homogeneity problems after powder discharge -Detect mechanical parameters critical in discharge component to avoid segregation along the falling	Physical parameters of raw materials: -Study individual particle size distribution of each API -Study particles morphology -Study density of each API -Evaluate the possibility of using other type of each API: options related to particle size, morphology and density

(continue next page)

Process Stage											**Remarks**
Encapsulation											*(continuation of previous page)* Mechanical parameters of gravimetric powder discharge: -pipe diameter -fall height -feeding rate -moisture -mixing ratio -insert presence in discharge pipe -Effect of interaction of these mechanical parameters with maintenance of blend's content homogeneity

Remark about Encapsulation Stage:

Beyond assay and content uniformity of each API, other quality parameters of filled capsules such as aspect, dimensions, individual weight, average weight, disintegration time, degradation products, and dissolution of paracetamol, were already tested in samples taken from the beginning, middle and end of filling process, for process validation purposes. All results were within specifications, so the encapsulation stage is considered to be validated.

Along routine manufacturing of this product these tests are always performed and all these parameters, except assay and content uniformity have been always within specifications.

Background data showed that there has been detected occasionally, some batches with a variability of content uniformity between the beginning and the end of filling process. This variability tend to be observed in Pseudoephedrine HCl and Chlorphenamine Maleate results, and can be reflected in assay results for these API's.

For these reasons, only assay and content uniformity parameters were considered to be relevant in this risk assessment for encapsulation stage.

Conclusions from FMECA:

According to the risk assessment performed through FMECA, the parameters with higher Risk Priority Number (RPN) are clearly the assay and content uniformity parameters in encapsulation stage. However, through this analysis it is also observed that these parameters are intrinsically related to content homogeneity after mixture powder discharge. Despite mixture stage is considered in control, this analysis shows how important is to improve knowledge about physical properties of each component of this formulation, specially of each API since they are the greater part of this formulation. It is necessary to explore the options for each API, in terms of density, particle size, and other properties relevant to segregation occurrence, as well as, the most relevant interactions between the different API's to achieve the desired flowability and content homogeneity, even when the mixture is subject to gravity forces along the gravimetric discharge.

Another important aspect of this process in the discharge of powder to the hopper of encapsulation machine. The way content homogeneity is maintained is critical to the success of filling process, in terms of content uniformity and assay of each API in capsules. If with manual discharge there were some content uniformity values so different between the beginning and the end of process, with gravimetric discharge this variability tends to increase because the falling enhances the differences between the different type of particles involved in the formulation, in terms of physical interactions. For this reason, it is necessary to improve knowledge about the mechanical properties present on the discharge system and understand how could those properties minimize the powder segregation effect.

In the next chapter, a process optimization will be proposed, having in mind all the parameters with higher criticality index (RPN) and respective actions required and remarks. In a rational basis, tests will be suggested, in order to elucidate how can a gravimetric discharge of the blend be performed, without increasing the variability observed in the current process.

5. DESIGN OF EXPERIMENTS

By definition, segregation is the tendency of particles to separate according to their individual physical properties. Segregation is a common effect verified often in solid pharmaceutical formulations [50]. A stage such as a gravimetric discharge is sufficient to promote the separation of the powder particles, with respect to their size and density. Therefore, when the blend reaches the hopper of the encapsulation machine, it can no longer be homogenized. This may be the reason why the content uniformity tests reveals so much variability.

5.1. Physical properties of raw materials

In the following table there is a description of the raw materials used in the product:

Description	Supplier
Paracetamol	Covidien Mallinckrodt
Dextromethorfan HBr	Divi's Laboratories
Chlorphenamine Maleate	Venkatarama Chemicals
Pseudoephedrine HCl	BASF
Pregelatinized Starch	Colorcon US
Magnesium stearate	Dr. Paul Lohmann
Silicon Dioxide	Degussa
Capsule nr 0	Qualicaps Europe

Table 10 – Product Raw Materials

Since in this formulation the 4 active substances are the major part and show such different physical properties from each other, it would be interesting to study them separately and understand the different options we have, in order to predict

their behavior in a mixture. Next, there is a review of the available raw data from all the results obtained in quality control analysis for batches of each active substance analyzed in 2008 [56]. The selected tests are those which concern to physical properties of raw materials.

Paracetamol

Paracetamol is the major active substance. A summary of the particle size and bulk density values obtained for paracetamol batches used in the manufacture of finished product batches in 2008 is given in Table 11.

Active Substance	**Raw Material Batch**	**Particle Size > 400 µm (max 1,0 %)**	**Particle Size > 150 µm (32,0 - 64,0 %)**	**Particle Size > 75 µm (14-29 %)**	**Bulk Density (g/cm^3)**
Paracetamol Dense	PA	*	*	*	0,814
	PB	*	*	*	0,726
	PC	*	*	*	0,801
	PD	*	*	*	0,686
	PE	0,00	48,7	20,90	0,708
	PF	0,00	50,1	19,93	0,726
	PG	0,00	48,4	21,3	0,714
	PH	0,00	53,5	20,32	0,735
	PI	0,00	50,8	22,75	0,782

Table 11 – Particle size and bulk density results for Paracetamol batches used in manufacture in 2008 [56]. **Information not available for these batches*

This data shows that Paracetamol has a constant particle size distribution between batches, but density values vary between 0,686 and 0,814 g/cm^3.

According to the Paracetamol supplier, Mallinckrodt, there could be other options for Paracetamol particle size and density (Table 12) [57].

Type of Paracetamol	***Particle Size (μm)*** ***Cumulative %***	***Bulk Density (g/ml)***	***Tapped Density (g/ml)***
Semi-Fine Powder	> 20 μm - ≈ 68% > 38 μm - Max. 45% >105 μm – Max.12% >250 μm – Max. 2%	0,26	0,53
Fine Powder	> 20 μm - ≈ 59% > 38 μm - 11-32% >105 μm – Max.9%	0,26	0,48
Dense Powder (used in the actual formulation)	> 20 μm - ≈ 98% > 75 μm – 46-94% > 150 μm - 32-64% > 250 μm - 30% > 420 μm - 1%	0,66	0,92

Table 12 – Physical properties of the 3 types of Paracetamol from Mallinckrodt [57].

Dextromethorfan HBr

Dextromethorfan HBr is the second major active substance in this formulation.

In Table 13 there is a summary of particle size results for the Dextromethorfan HBr batches used in the manufacture of finished product batches in 2008. There is no information on particle size distribution for the Divis batches, but from data of DSM batches (previous supplier), particle size distribution seems to be similar between batches.

		Particle Size Distribution		
Active Substance	**Raw Material Batch**	**Percentil 10 (0-110 µm)**	**Percentil 50 (0-200 µm)**	**Percentil 90 (0-300 µm)**
Dextromethorfan Bromidrate (Divis)	DA	*	*	*
	DB	*	*	*
Dextromethorfan Bromidrate (DSM)	DC	61	136	231
	DD	62	139	235
	DE	61	136	231
	DF	58	134	225

Table 13 – Particle size distribution results in Dextromethorfan Bromidrate batches used in manufacture in 2008 [56]. **Information not available for these batches*

There were studies performed in Lusomedicamenta (LM) to compare how Dextromethorfan HBr from two different suppliers worked in the formulation and in capsules dissolution testing, and they were considered equivalent [58]. For the following experiments only Dextromethorfan HBr from Divis will be considered, because Divis is the current supplier.

Pseudoephedrine HCl

In Table 14 a summary of the physical properties analysed for the Pseudoephedrine HCl (Fine Powder) batches used in the manufacture of the same finished product batches in 2008 is given.

Active Substance	**Raw Material Batch**	**Particle size < 150 µm (min 97%)**
Pseudoephedrine Hydrochloride	EA	100
	EB	100
	EC	100
	ED	100
	EE	100
	EF	100
	EG	100
	EH	100

Table 14 – Particle size results for Pseudoephedrine HCl (Fine Powder) batches used in manufacture in 2008 [56].

More physical tests, for example particle size distribution, flowability, angle of repose, density and bulk density, would be useful to understand the behaviour of Pseudoephedrine HCl in the blend.

There are 5 types of Pseudoephedrine Hydrochloride, from BASF which is the actual supplier of this active substance for the referred process [59]. The main differences between them are summarized in Table 15:

Type of Pseudoephedrine HCl	***Particle Size (μm)***	***Bulk Density (g/ml)***	***Tapped Density (g/ml)***
Fine Powder (used in the actual formulation)	< 150 μm - ≥ 97%	0,28	0,34
Coarse Powder	< 425 μm - ≥ 97% < 45 μm - ≤ 60%	0,42	0,55
Crystalline	< 500 μm - ≥ 99% < 106 μm - ≥ 15%	0,68	0,74
Crystalline 60/140	< 500 μm - 100% < 250 μm - 50-95% < 106 μm - ≤ 15%	0,67	0,77

Table 15 – Particle size, tapped density and bulk density values for 5 types of Pseudoephedrine HCl from BASF [59].

Having a larger particle size, for example with Pseudoephedrine Coarse Powder or Crystalline, there would be less probability of segregation, without compromising the bio-availability, since Pseudoephedrine HCl is easily soluble. Enlarging the particle size of this active substance would also decrease the possibility of dust clouds during gravimetric discharge and the formation of conglomerates because with larger particle size there would be a smaller specific surface, therefore a smaller tendency for moisture absorption.

Chlorphenamine Maleate

Chlorphenamine Maleate is another active substance in this formulation. In Table 16 there is a summary of the particle size results for the Chlorphenamine Maleate batches used in manufacture of finished product batches in 2008:

			Particle Size Distribution			
Active Substance	**Raw Material Batch**	**Particle size ≤ 500 µm (Min 85%)**	**Percentile 10 (0-110 µm)**	**Percentile 50 (0-200 µm)**	**Percentile 90 (0-300 µm)**	**Percentile 100 (0-300 µm)**
Chlorphenamine Maleate	CA	100	< 3,90	< 21,32	< 63,89	< 140,58
	CB	100	< 3,76	< 26,12	< 99,24	< 190,80
	CC	100	< 3,95	< 25,89	< 91,81	< 163,77
	CD	100	< 3,94	< 32,85	< 109,83	< 190,80
	CE	100	< 3,76	< 26,12	< 99,24	< 190,80
	CF	100	< 5,14	< 44,33	< 150,45	< 301,68
	CG	100	< 4,49	< 42,19	< 154,34	< 301,68

Table 16 – Particle size results for Chlorphenamine Maleate batches used in manufacture in 2008 [56].

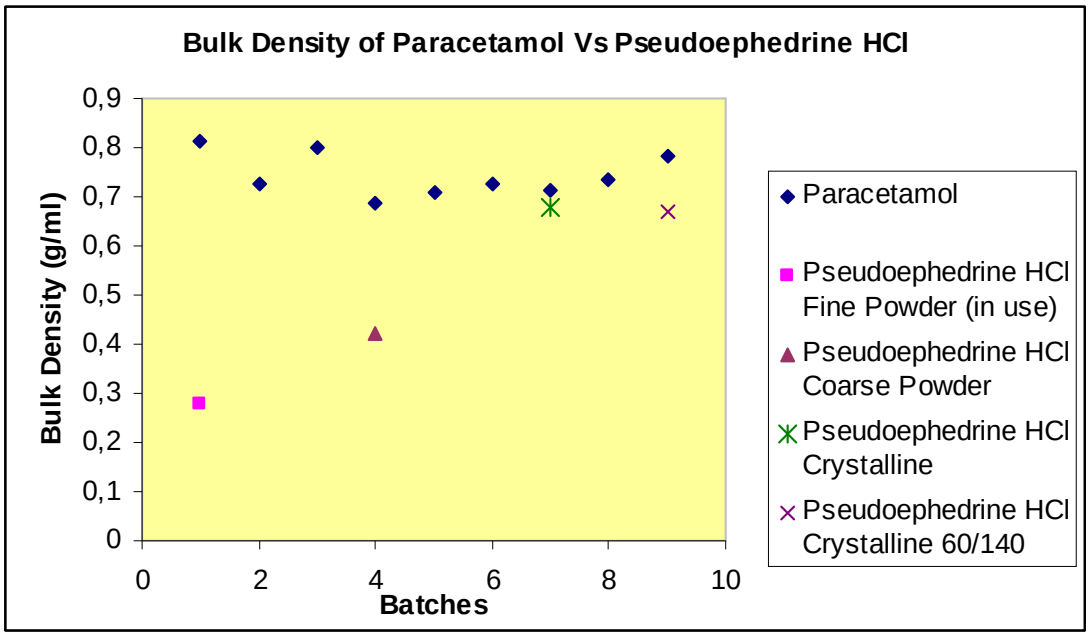
These data show that particle size distribution, in particular percentile 50 diverges between 21 and 44 µm. Percentile 100 is dispersed between 140 and 301. This means the particle size has a wide distribution range. Furthermore, the batches CF and CG show a larger difference between the smaller particles and the bigger ones, which can induce a different behaviour in a blend with the other components.

Conclusions from Active Substances data review

Paracetamol Dense Powder is the type of Paracetamol currently used in this formulation. According to options showed in table 12, with Paracetamol Semi-Fine Powder or Paracetamol Fine Powder there would be a smaller particle size for this

active substance and density values would be closer to the density of Pseudoephedrine HCl (table 15), for example. However, decreasing Paracetamol density is not an option because it would require a change of the capsule size for a bigger one. That would be a relevant change, which is not the purpose of this study.

On the other hand, Paracetamol Dense Powder (currently used) has a higher bulk density than most of the 4 options for Pseudoephedrine HCl. Nevertheless, with Pseudoephedrine Crystalline or Pseudoephedrine Crystalline 60/140, the difference between the density of these 2 active substance would be minimized (Graph 9).



Graph 9 – Bulk density of paracetamol compared with the bulk density of the different types of pseudoephedrine HCl from BASF [56, 59].

In respect to particle size, Pseudoephedrine Crystalline 60/140 has a particle size range closer to that on Paracetamol Dense Powder (Table 17).

Type of Active Substance	Minimal Particle Size (μm)	Maximum Particle Size (μm)
Pseudoephedrine HCL Fine Powder *(in use)*	30	150
Pseudoephedrine HCL Coarse Powder	45	425
Pseudoephedrine HCL Crystalline	30	106
Pseudoephedrine HCL Crystalline 60/140	106	250
Paracetamol Dense Powder	75	250

Table 17 – Approximate minimum and maximum particle size for Paracetamol Dense Powder and each type of Pseudoephedrine HCl available from BASF.

For Dextromethorphan HBr and Chlorphenamine Maleate there is very few information, so it is necessary to perform more tests to understand in more detail particle size range and density values for each of these active substances.

Tests to identify the critical parameters of each active substance:

The physical properties that are known to induce segregation are the particle size, morphology, bulk density and tapped density, cohesivity, friction, surface texture, the modulus of elasticity and coefficient of restitution. First, a set of tests to detect all the relevant physical properties would be useful to improve the knowledge about these 4 active substances individually:

- particle size
- particle morphology
- bulk density
- tapped density
- surface texture
- cohesivity
- repose angle
- flowability rate

These tests should be performed in 10 different batches of each possible type of active substance.

Paracetamol Dense Powder (Mallinckrodt)	**Dextromethorfan HBr (DSM)**	**Pseudoephedrine HCl (BASF)**	**Chlorphenamine Maleate (Venkatarama Chemicals)**
		Coarse Powder	
		Crystalline	
		Crystalline 60/140	

Table 18 – Types of active substances to be tested.

The flowability rate, the repose angle and cohesivity should be considered as quality variables. The other properties should be considered as operative variables since they are parameters that can be chosen when buying them and tested before use in the process.

Operational Variables	Quality Variables
Particle size	Flowability rate
Particle shape	Repose angle
Bulk density	
Tapped density	Cohesivity
Surface texture	

Table 19 – Operational and Quality Variables for chemometric study.

A chemometric study of all data collected, performed with an adequate software (SIMCA from Umetrics, e.g.) would establish the relationship between these variables and clarify the influence of each of them in the final conditions of flowability and repose angle which will be determinant to the behaviour of the actives substances in the formulation. This study would enhance not only the critical

parameters of each active substance, but also show which of these properties are not relevant and could be discarded in the following experiments.

For formulation tests there will be the following hypothesis:

Formulation 1 (actual formulation)	**Formulation 2**	**Formulation 3**	**Formulation 4**
Paracetamol Dense Powder	Paracetamol Dense Powder	Paracetamol Dense Powder	Paracetamol Dense Powder
Dextromethorfan HBr	Dextromethorfan HBr	Dextromethorfan HBr	Dextromethorfan HBr
Pseudoephedrine HCl Fine Powder	Pseudoephedrine HCl Coarse Powder	Pseudoephedrine HCl Crystalline	Pseudoephedrine HCl Crystalline 60/140 Powder
Chlorphenamine Maleate	Chlorphenamine Maleate	Chlorphenamine Maleate	Chlorphenamine Maleate
Pregelatinized Starch	Pregelatinized Starch	Pregelatinized Starch	Pregelatinized Starch
Colloidal Silicon Dioxide	Colloidal Silicon Dioxide	Colloidal Silicon Dioxide	Colloidal Silicon Dioxide

Table 20 – Plan of different formulations to be tested.

5.2. Gravimetric discharge critical parameters

The physical conditions how gravimetric discharge is performed is another important aspect of this study. There are conditions which can be measured and controlled along the process, and there are parameters of the mechanical system which can be modified, in order to improve the homogeneity of the mixture during the discharge.

These tests will focus only on the discharge stage. In all produced batches, the content homogeneity of the final blend had always reproducible data, within specifications before the gravimetric discharge. Therefore, the blending stage is considered a controlled process.

The mechanisms of segregation are related with different process conditions such as vibration, fluidization, pouring in a heap, fall height, feeding rate, moisture

and mixing ratio. The primary mechanisms of segregation are percolation (sifting or void filling), trajectory (rolling), fluidization, push-away effects, angle of repose and stratification [50]. The presence of an air stream inside the discharge tube, flowing against the mixture, and the type of material with which the discharge tube is covered, may also influence the segregation phenomena.

For the study of critical parameters of gravimetric discharge it is proposed a design of experiments where the gravimetric discharge will be simulated as it happens in the industrial process, using the formulation as it is registered. The simulation should be performed with a scale-down apparatus made with all the characteristics of the real situation for gravimetric discharge, in terms of measures, positions of the different parts involved (except the encapsulation machine), and where it is possible, the nature of construction materials. In terms of scale it could be similar to the ASTM device used to this kind of tests (ASTM D 6940-04 Segregation tester) [50]. However, there must be also the possibility of changing parts to conduct the set of proposed tests.

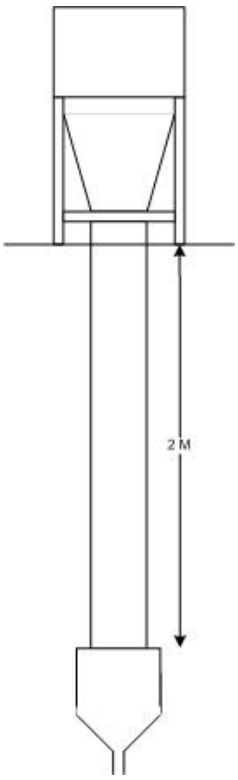


Figure 10 - Representation of elements present in a gravity discharge situation: Blend's IBC in the first floor, discharge pipe, hopper of encapsulation machine in the ground floor.

The operational variables tested would be:

- pipe diameter
- fall height
- feeding rate
- moisture
- mixing ratio
- insert presence in discharge pipe

These properties are measurable and can be controlled with appropriate devices along the system.

The quality variable would be the ratio between the average content homogeneity obtained for the first sample taken from the collected blend at the beginning of gravimetric discharge, and the average content homogeneity for last sample taken at the end of discharge. From hereon, this quality variable will be referred as CH ratio.

$$\frac{\text{Content Homogeneity}_{(\text{first sample collected})}}{\text{Content Homogeneity}_{(\text{last sample collected})}} = \text{CH ratio}$$

The proposed quality variable CH ratio represents a measure of homogeneity of the mixture after being subject to gravimetric discharge. The content homogeneity test would be performed as it is established in the pharmaceutical product MA Dossier, in the quality control analytical procedures chapter. A sampling plan with 5 points is proposed for the samples taken at the beginning and the end of the discharge. This figure was drawn having in mind that after the discharge, the mixture will have approximately the form of a pyramid:

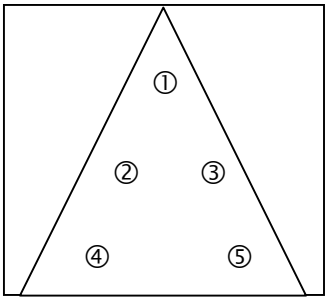


Figure 11 - Proposed sampling plan for content homogeneity tests.

The closer to 1 this CH ratio is, the better is the content homogeneity of the mixture after the discharge. This would be sufficient to show some difference present in the final mixture, because according to recorded data from the batches produced (part 3.4.), usually tests of content uniformity of filled capsules usually indicate higher levels of Pseudoephedrine HCl at the beginning of filling, tending to decrease along the filling, ending with capsules with much less Pseudoephedrine HCl content. This happens also with the content of Chlorphenamine Maleate, in some batches. These two active substances are the smallest in particle size, and differ considerably from the other components of this formulation. One of the objectives of these tests is to understand if there are any properties in the mechanical part of the discharge process that can minimize this segregation effect.

MODDE is a software from Umetrics very useful in this kind of studies, not only to plan the experiments (DOE) but also for chemometric data processing and to obtain 3D representations of DOE and its results. After data processing, it is expected to know which are the principal components in the mechanical part of the gravimetric discharge system and how they must be set, to minimize the tendency of segregation.

The next stage will involve using the optimized discharge system in scale-down, build a design of experiments to study the effect of the several different types of formulations, how their components interact along the gravimetric discharge and decide what could be the best formulation in order to achieve the desired quality in filled capsules.

5.3. Process Optimization

With the results obtained from part 5.1. of this study, there is a greater knowledge about the physical nature of each active substance present in this formulation. It would be possible now to choose definitely the more similar 4 active substances to interact with each other, in terms of physical properties. Next, it would be necessary to study the physical properties of the actual formulation and the 4 formulations proposed at the end of part 5.1..

Formulation 1 (actual formulation)	**Formulation 2**	**Formulation 3**	**Formulation 4**
Paracetamol Dense Powder	Paracetamol Dense Powder	Paracetamol Dense Powder	Paracetamol Dense Powder
Dextromethorfan HBr	Dextromethorfan HBr	Dextromethorfan HBr	Dextromethorfan HBr
Pseudoephedrine HCl Fine Powder	Pseudoephedrine HCl Coarse Powder	Pseudoephedrine HCl Crystalline	Pseudoephedrine HCl Crystalline 60/140 Powder
Chlorphenamine Maleate	Chlorphenamine Maleate	Chlorphenamine Maleate	Chlorphenamine Maleate
Pregelatinized Starch	Pregelatinized Starch	Pregelatinized Starch	Pregelatinized Starch
Colloidal Silicon Dioxide	Colloidal Silicon Dioxide	Colloidal Silicon Dioxide	Colloidal Silicon Dioxide

Table 21 – Plan of different formulations to be tested.

These physical tests would be those which showed to have a major contribution to powders' best flowability. The differences between the results observed with the actual formulation and proposed formulations must be compared and evaluated. From part 5.2., there are also some mechanical aspects within the gravimetric discharge that have shown to be critical to keep the mixture homogeneous even after falling down the discharge pipe to the hopper of

encapsulation machine. A new model should be constructed using those properties, still in scale-down, to test the actual formulation and the other 3 proposed formulation, in 3 batches from each formulation.

The results should be translated again as the ratio of the content homogeneity test of the first sample taken and the last sample taken after the discharge.

Another test which would be interesting is the observation of the different results obtained when the mixture of all components of the formulation, the current and the 3 proposed formulations, are subject to granulation before the discharge. This is not a common stage in this kind of pharmaceutical preparation, since it would take more time and firstly seems to be dispensable. However, due to the difference of particle size and density of the components, and the apparent lack of homogeneity control along the discharge, perhaps this option should not be discarded. The quantitative result (quality variable) would be again the CH ratio as described before.

Proposed DOE - Factorial Design 2^5:

Operational Variables	Quality Variable
Blend and Gravimetric discharge with Formulation 1	$\frac{\text{Content Homogeneity}_{(\text{first sample collected})}}{\text{Content Homogeneity}_{(\text{last sample collected})}} = \text{CH ratio}$
Blend and Gravimetric discharge with Formulation 2	
Blend and Gravimetric discharge with Formulation 3	
Blend and Gravimetric discharge with Formulation 4	
Blend, Granulation and Gravimetric discharge with Formulation 1	

Table 22 – Proposed DOE for process optimization study.

All data collected should be processed with a software like MODE or SIMCA, used in previous experiments (part 5.1 and part 5.2.), integrating the information taken from each statistical representation. This stage of the study aims to assess if

there can be a significant difference in the mixture uniformity results obtained with another formulation after gravimetric discharge and if it would be relevant to perform a granulation stage in order to standardize the particle size of all components.

According to these conclusions, an optimized gravimetric discharge model should be constructed in real scale. The final tests should be performed in a pilot-scale batch, where all the process should be run from the blend of all components up to capsules filling. There should be a batch with the usual formulation, and a batch made with the best new option for formulation. Then, finished product quality control tests should be performed to both batches and compared. One important aspect of finished product, for its quality and effectiveness on patients is the dissolution rate and its profile, and that is why there must be a comparative study of both formulations which must assure the same pharmaceutical behavior.

6. REVALIDATION STRATEGY AND NEW TECHNOLOGIES FOR CONTROL

Despite one of the goals of this project being the proposal of a planning for a optimization of the process with minimal changes to what is already registered, the results obtained should be observed in order to find if the specifications should be altered in some stage of the process, for example, narrowing the accepted limits for blend homogeneity after discharge. When there is a wide range of particle size distribution between the different components in a blend and there is no stage of the milling or granulation, segregation is likely to arise. The difference of particle size and density between components could be minimized if there would be a dry or wet granulation process between the blending and the gravimetric discharge. On the other hand, the lack of choice related to physical properties of Paracetamol is another limitation of this process as it's grade is registered. Moreover if density of Paracetamol was reduced in order to be more similar to the density of the other active substances, a bigger capsule size would be necessary and that would be considered a change with high regulatory impact. Another possibility to solve this difference of particle size and density between the components of this formulation and consequent content homogeneity variability, would be to change the pharmaceutical presentation to tablets instead of capsules, for example. But all these options would result in a change of the formula and would require a new submission of MA.

If there is the possibility to carry out a process optimization within the previous design space, the whole process must be therefore revalidated with industrial batches, and its reproducibility, robustness and efficiency should be demonstrated. Usually this phase of a project is performed with 3 industrial batches, but according to FDA's new guideline for industry on process validation [1], the number of batches is left to be decided by the product manufacturer. The major goal here is that the manufacturer understands and has the sufficient knowledge about the process, so he can justify how many batches are necessary to show the process is in control and to assure routine finished product quality, based on a scientific rational and statistical analysis.

PQLI is a concept created to help the implementation of guidance ICH Q8, ICH Q9 and ICH Q10. QbD is a concept introduced by guidance ICH Q8 for pharmaceutical development, which promotes product and process understanding based on scientific knowledge and quality risk management. Through QbD, manufacturers can concentrate their control efforts on the critical parameters to quality. Another asset of QbD is to enable continuous improvement of the design space without any further regulatory review, which is the main objective of this thesis. For this to become possible, there must be a team work between several areas in a company, from quality control to process development to manufacturing and quality assurance, working in the framework of the process design space.

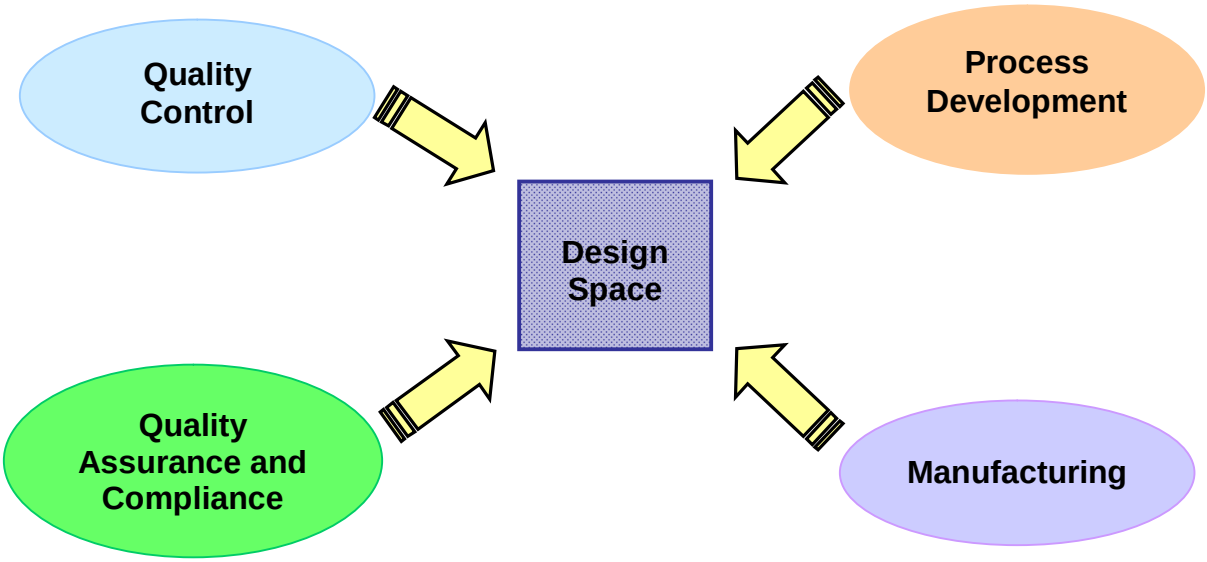


Figure 12: Team work with Design Space as framework.

QbD can also promote the use of new technologies and the use of new approaches to perform process validation, such as continuous quality verification along product lifecycle.

In part 3 of this thesis the background knowledge of this process was reviewed, as well as the analytical data that have been collected in terms of content uniformity and assay results for the 4 active substances in this formulation.

In part 4, following ICH Q9 guidance, a risk assessment analyses was performed in order to establish the critical stages of the process. Through FMECA the process critical parameters were distinguished at multiple levels. Those levels, according to their Risk Priority Number (RPN), represent their impact in final product quality, probability of occurring, severity of their consequences or its sensitivity in terms of capacity to detect failures with the control strategy currently used. As ICH Q9 refers, while process understanding increases during a product lifecycle, the criticality is an interactive process to re-evaluate the risk inherent to process variables and quality attributes. This means critical parameters can change along the lifecycle of the product and that will be detected with the continuous quality verifications proposed by the new FDA guidance on process validation. Based on risk assessment conclusions, assay and content uniformity of filled capsules are the parameters with higher RPN. However, through this analysis it was also observed that these parameters are intrinsically related to content homogeneity after mixture powder discharge. Following this logic, it is important to explore the physical characteristics of each API that can contribute to segregation incidence throughout the gravity discharge. The mechanical parameters present in gravity discharge equipment are also relevant to understand powder mixture behavior along the discharge.

In part 5, a plan of experiments was proposed to define the CQA's of the active substances used and the CQA's for gravimetric discharge, in order to achieve a broader understanding of the discharge process. Again, those CQA's are not static and may change their criticality as the process is improved with the continuous quality verifications.

The Design Space is a multidimensional combination and interaction of input variables and process operating parameters that have proved to be relevant for quality assurance. These could be the CQA's and CPP's concluded from the experiments suggested in part 4 and 5 of this thesis. The intention is to integrate a design space well performed together with an appropriate control strategy that will support the consistency of the process and the robustness of its results. In this stage engineering solutions should be adopted for equipments, for materials and for facilities, in order to maintain the process within the design space.

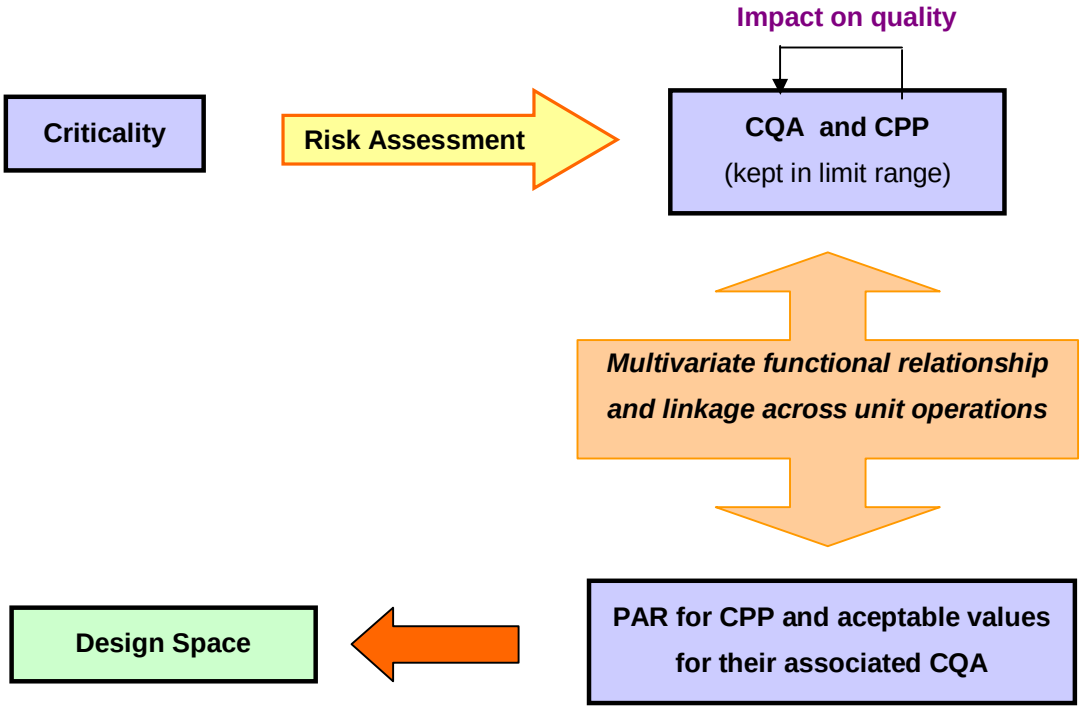


Figure 13: Readjustment of Design Space through Criticality and risk assessment.

A control strategy should control the process' risks to the degree that they might exceed the limits of the design space. Therefore, the CPP's and the CQA's included in the design space must be also included in control strategy. According to guidance ICH Q10, control strategy is a planned set of controls derived from the process and product knowledge that assures process performance and product quality. Based on that, control strategy may include API purchase specifications, according to CQA's detected in experiments suggested in part 5.1.. This strategy may include also operating ranges for process parameters, release testing and API or product specifications and their acceptance criteria.

ISPE has proposed a model to PQLI control strategy which links product attributes important to patients in parallel with those to business requirements. According to that model, control strategy should be subdivided in 3 levels. Next, an adaptation to that model is proposed.

Control Strategy – Level 1

This level is reserved for identification of CQA's of the active substances or finished product, which are related to patient safety, efficacy and quality (derived from PTPP). In parallel, in the business area parameters such as the cost, efficiency, operator safety, manufacturability and supply related objectives are included. For example:

- API's: CQA's detected in experiments suggested in part 5.1.
- Finished product: CQA's could be the appearance, dissolution rate, active substances assay, content uniformity, capsule closure, dimensions, for example.

Control Strategy – Level 2

This level is for CQA's of raw materials, solvents and reagents included in the process that must be monitored or controlled and operating conditions of process equipment that have to be monitored or controlled to ensure the objectives established in level 1.

Control Strategy – Level 3

In this level the main concern is the analytical and other control methods, as well as measurement technologies for material attributes or equipment parameters. Those controls can be off-line, at-line, in-line or on-line, multivariate process models and control models, normal operating ranges and alarms. Level 3 should also describe what the process control models will do and how they will be operated and maintained, within the PQS of the company.

To verify if the process is under control, there must be a set of quality control tests to run along the process as in-process controls (IPC), how it is usually done in a validation process, according to critical stages of this process:

- at the end of the blending stage, for content homogeneity of the 4 active substances;

- at the end of gravimetric discharge stage before the filling, for checking the content homogeneity of the 4 active substances;

- and in periodic samples during the encapsulation process, for verify the content uniformity of the 4 active substances in capsules.

The sampling plan could be maintained as it was before, except at the IPC after discharge, where samples could be taken from the hopper of encapsulation machine along filling process, while the powder mixture is being discharged. The intention is to check the content homogeneity at the beginning, at the middle and in the end of discharge. It would be taken 5 samples in 3 different stages of discharge. These 15 samples pretend to show a wider screen from the mixture along the discharge, before the process moves towards a no satisfactory content uniformity result in filled capsules. In Figure 14 there is a representation of the 5 sampling points.

1) left upper side;
2) right upper side;
3) left middle side;
4) right middle side;
5) discharge bottom.

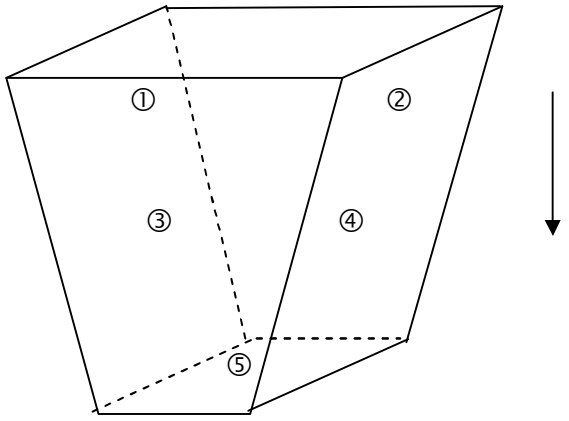


Figure 14: Sampling points in the hopper of encapsulation machine.

The IPC results of the content homogeneity and content uniformity should be compared in terms of average, standard deviation and relative standard deviation, for each active substance.

The extended evaluation of analytical data done in 2005 [52], and the results collected from batches manufactured in 2008 [54], demonstrated how the content uniformity of one active substance is related to its assay result in the finished product. When the content uniformity test shows an high value for relative standard deviation in one of the active substances (most of times Pseudoephedrine HCl), the assay result is closer to upper limit.

Pseudoephedrine HCl content uniformity values are those which have more variability between the beginning and the end of a batch. This is clearly the more concerning active substance in this formulation, so its assay should be observed carefully along the process.

These process controls have always been out-line and off-line which means there is always a technician who does the sampling and takes the samples to the quality control laboratory where the chemical tests are performed, while the process is paused waiting for results.

Following the latest guidance about process controls and analytical technology [43, 44, 48], this has the tendency to be done in-line and on-line. The controls can be made without taking samples off the IBC's, but with probes inserted in the devices where the process is occurring. PAT reduces the human factor in the process, the logistics needed for carrying the samples to the laboratory and the time, means and consumables needed for analysis and increases the knowledge of the process. These controls tend to be on-line which means the analysis and its data processing is made through software capable of giving results in real time of the variable measured and adjust the process. Moreover, these results are automatically processed with the rest of data from the same process. It is also possible to have control charts with process evolution through time, in terms of one variable that needs control or even its influence on other variables. Another advantage of PAT is the possibility to react to the state of process, and the capability to correct something out of control without waiting until a final stage where the process is irreversible.

Probably the most common analytical technique used in PAT is the Near Infrared spectroscopy (NIR), because it provides major advantages over conventional methods, because it neither requires sample preparation, nor the

damaging of samples during the tests. In combination with chemometrics, FT-NIR enables quantitative analysis of a pharmaceutical preparation. It is also considered to be a technique which permits to distinguish the chemical and physical properties of samples. This means FT-NIR enables the identification and assay of active substances in solid state and liquid state, and at the same time is sensitive to moisture increase in mixtures or the compressibility of a mixture. Since gravimetric discharge is one of the most critical stages of the process, it would be interesting to implement a PAT system in the hopper of the encapsulation machine, in order to test content homogeneity of the blend.

In 2008, a study on FT-NIR spectroscopy and Laser Diffraction particle sizing of API's in pharmaceutical formulation was performed [60]. The formulation studied was composed of Paracetamol, Dextromethorfan and Pseudoephedrine HCl in the same percentage as the formulation referred in this thesis. One of the observations in that study was the overlapping of several absorption bands in the FT-NIR spectra of the 3 API's, due to similarities in their chemical structure, i.e. the aromatic rings. That effect was more evident between Paracetamol and Pseudoephedrine HCl, as can be observed in the following figures.

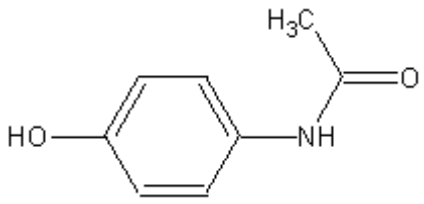


Figure 15 - Paracetamol

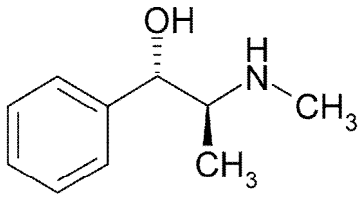


Figure 16 - Pseudoephedrine HCl

According to that study, the lack of selectivity problem could be solved with multivariate chemometrics techniques as Partial Least Squares regression, without overlapping absorption bands between Paracetamol and Pseudoephedrine HCl.

In the same study [60], FT-NIR and powder laser diffraction showed to be efficient to identify differences between physical properties of samples, such as the

active substances' particle size distribution. Powder laser diffraction is a useful analytical tool for the particle characterization of active substances, since it can be precise over a wide particle size range. According to tests performed on that study, Paracetamol has a particle size distribution more similar to Dextromethorfan HBr, than to Pseudoephedrine HCl.

In the study referred before [60], calibration models were developed to quality control purposes on that pharmaceutical formulation, using FT-NIR. The absolute error of each API was calculated to demonstrate the potentiality of the proposed method. However, despite being possible to detect the 3 active substances with small errors, the error associated to Dextromethorfan HBr and to Pseudoephedrine HCl is too high for analytical application in a pharmaceutical blend. The best calibration model gave an error of 10% for Pseudoephedrine HCl and 12,5% for Dextromethorfan HBr detection.

According to guidance on powder blends the content homogeneity of an active substance in a blend must be within 90%-110% limit [61], so the FT-NIR spectroscopy is not the best option as an accurate analytical tool for a PAT system at the end of the gravimetric discharge with this formulation.

There is also Raman spectroscopy, which consists in measuring the vibrational frequencies of various parts of a molecule. The 'pattern' of vibrational frequencies from a molecule is, therefore, highly characteristic of a given molecular species and, for solid samples, of the crystalline arrangement of those molecules. Raman spectra may be readily recorded from gases, liquids and solids. While IR spectroscopy is essentially based on illuminating the sample with a broad range of wavelengths of IR light and measuring which are absorbed, a Raman spectrum is obtained by illuminating the sample with a single wavelength of light from a laser and collecting and analysing the resulting scattered light. NIR and Raman can be complementary from each other. While some molecular vibrations may be observed in both the IR and the Raman spectra, often vibrations observed using one technique will be extremely weak or totally absent in the other. The features in the Raman spectrum corresponding to the various vibrational modes of a molecule are generally sharp, well resolved and, for many active pharmaceutical compounds, numerous. This is why Raman spectroscopy can be used for different polymorph detection,

identification of raw materials and also to verify the content homogeneity of mixtures [62, 63]. This makes Raman spectroscopy an option for pharmaceutical PAT applications, like the analysis of a powder mixture, and one of its advantages is its flexibility of implementation in-line at a manufacturing environment.

In cases where lower concentrations of drug substance are present, Light – Induced Fluorescence is more powerful than NIR or Raman. One situation where this technique is being used is as a PAT tool for the analysis of blend uniformity of a mixture, prior to either compression or granulation [64]. This means that could be a good candidate for a PAT system to implement in the hopper of encapsulation machine, to test content homogeneity after the gravimetric discharge. Because of lack of structural information, Fluorescence Spectroscopy can be combined with other analytical techniques such as Nuclear Magnetic Resonance NMR or FT-IR spectroscopy. Nevertheless, these last options are a more expensive solution, not only in terms of implementation, but in maintenance of the equipments required for those systems.

Only with experiments and simulations of calibration models in chemometric systems, a suitable analytical technique can be determined. This analytical tool must take into account the small percentage of the APIs in the formulation, namely the Dextromethorfan HBr, the Pseudoephedrine HCl and the Chlorphenamine Maleate. Another issue to take into account is the narrow acceptance limits established by guidances, according to the stage of process and the type of test to be performed.

In summary, the control strategy must be implemented within a framework comprising the PQS and GMP, and also within environmental health and safety systems together with financial and business related aspects.

CONCLUSIONS

In November 2008, United States Food and Drug Administration (FDA) has launched for public discussion the draft of the "*Guidance for Industry Process Validation: General Principles and Practices*" which will bring a new approach of the actual concept of process validation, toward the concept of product lifecycle time. Having the scientific knowledge as its basis, this guidance encourages the voluntary development of innovative manufacturing, process optimization and quality assurance approaches. FDA believes that Process analytical Technology (PAT) can be a "win-win" opportunity for both FDA and industry. The optimal application of modern analytical techniques in–process can reduce the rate of recalls, increase the efficiency of manufacturing and quality control, and provide a better scientific and engineering foundation.

The subject of this thesis consisted in a review of the principles and procedures concerning to pharmaceutical process validation in compliance with the Guidance for Industry Process Validation: General Principles and Practices (draft launched by FDA in November 2008), integrating the principles of the ICH Q8, ICH Q9 and ICH Q10 guidance, with the new guideline of FDA on pharmaceutical industry process validation. The industrial process of a commercialized product composed of a mixture of 4 active substances formulated in capsules was studied. Currently the manufacturing process consists of raw materials sieving followed by a blending stage, where all the active substances and excipients are mixed. The filling operation is performed in an intermittent motion capsule filler with a low output, and manual feeding by the operator, since homogeneity was compromised at gravimetric discharge in high speed capsule filling machines. However, even with manual feeding of encapsulation machine, this industrial process presents a batch to batch content uniformity variability of some of their active substances in finished product analysis. This problem was observed occasionally in some batches, but the results of the analysis of finished product did not show a clear relationship with neither an earlier stage of the process, nor any raw material physical characteristic that could have lead to the observed variability. It's known that whenever there is a wide range of particle size distribution of the components in a blend and there is no additional milling or granulation stages, segregation is likely to arise. The difference of particle

size and density between components could be minimized if there would be a dry or wet granulation process between the blending and the gravimetric discharge. Additionally, the density of Paracetamol cannot be reduced, because it would require a bigger capsule size. Another possibility to solve this difference of particle size and density between the components of this formulation and consequent content homogeneity variability, would be to change the pharmaceutical presentation to tablets instead of capsules, but all these options would result in major regulatory changes and would require a new submission of MA.

The main purpose of this thesis was to propose a new approach for process revalidation integrated with the lifecycle of this pharmaceutical product. This means that this new approach have taken into account principles from ICH 8, ICH Q9 and ICH Q10 guidance. This could be achieved through integration of knowledge and background data from Manufacturing, Quality Control, Quality Assurance and Process Development areas. Since this was a process of an existing commercialized product, the aim of this work was to propose a new approach to planning a process optimization with minimal changes and consequent process revalidation. The objective was to perform blend's gravimetric discharge, instead of manual feeding, to the encapsulation machine, without increasing the variability observed in the current process. A risk assessment (FMECA) was performed to evaluate the most critical parameters in this process and, based on their criticality index, an experimental design has been proposed, subdivided in three aspects.

a) Physical characterization of active substances;

b) Definition of the critical parameters of the gravimetric discharge system;

c) The design of experiments where the critical parameters of the active substances and the gravimetric discharge system are tested together, in order to define the optimized process.

If there is the possibility to carry out a process optimization within the previous design space, the whole process should be therefore revalidated with industrial batches, and its reproducibility, robustness and efficiency should be demonstrated. The number of batches should be as much as necessary to show the process is in

control and to assure routine finished product quality, based on a scientific rational and statistical analysis.

Product Quality Lifecycle Implementation (PQLI) is a concept created to help the implementation of guidance ICH Q8, ICH Q9 and ICH Q10. QbD is a concept introduced by guidance ICH Q8 for pharmaceutical development, which through manufacturers can concentrate their control efforts on the critical parameters to process quality and continuous improvement of the design space without any further regulatory review, and that is what this thesis intend to propose. The Design Space is a multidimensional combination and interaction of input variables and process operating parameters that have proved to be relevant for quality assurance. Therefore, the design space must be integrated with an appropriate control strategy, which controls the process' risks to the degree that they might exceed the limits of the design space. This means the Critical Process Parameters (CPP) and the Critical Quality attributes (CQA) must be either included in the design space and in the control strategy.

ISPE has proposed a model to PQLI control strategy which links product attributes important to patients in parallel with those to business requirements, in 3 levels. According to this, an adaptation of that control strategy model to this process was suggested:

1) *Level 1*: identification of CQA's of the active substances, as proposed in section 5.1.. In parallel, in the business area parameters such as the cost, efficiency, operator safety, manufacturability and supply related objectives for the product.

2) *Level 2*: controls for CQA's of raw materials, solvents and reagents that must be monitored or controlled and operating conditions of process equipment that have to be monitored or controlled to ensure the objectives established in level 1.

3) *Level* 3: analytical and other control methods, as well as measurement technologies for material attributes or equipment parameters. Those controls can be off-line, at-line, in-line or on-line, multivariate process models and control models, normal operating ranges and alarms. This

stage of control strategy should also mention how those controls will be operated and maintained within the Pharmaceutical Quality System (PQS) of the company.

To verify if the process is under control, there should be a set of quality control tests to run along the process as in-process controls (IPC), according to critical stages of this process:

- at the end of the blending stage, for blend uniformity of the 4 active substances;

- at the end of gravimetric discharge stage before the filling, for checking the blend uniformity of the 4 active substances;

- and in periodic samples during the encapsulation process, for verify the content uniformity of the 4 active substances in capsules.

The sampling plan could be maintained as it was before, but there should be taken 5 samples from the hopper of encapsulation machine at the beginning, at the middle and at the end of filling process, while the powder mixture is being discharged. This way there will be a broader knowledge on the content homogeneity through the gravity discharge. The IPC results of the blend homogeneity and content uniformity should be compared in terms of average, standard deviation and relative standard deviation, for each active substance.

Pseudoephedrine HCl content uniformity values are usually those which have more variability between the beginning and the end of a batch. Therefore, its assay should be observed carefully along the process.

These controls tend to be on-line associated with a PAT system, which means the analysis and its data processing is made through software capable of giving results in real time of the variable measured and adjust the process. Since gravimetric discharge is one of the most critical stages to the content homogeneity of the blend, it would be interesting to implement a PAT system in the hopper of the

encapsulation machine. Despite FT-NIR is one of the most common analytical techniques for PAT, a previous study [60] demonstrated that FT-NIR is not a suitable tool for quantitative analysis of active substances in this pharmaceutical formulation, after blend's gravimetric discharge. The error associated to that quantification is too high, comparing to the limits established by blend assessment guidance [61]. From several options presented, Raman spectroscopy could be an option for implement a PAT system in the hopper of encapsulation machine. It would be interesting to explore the potential of this analytical tool for verification of the content homogeneity of the powder mixture after gravimetric discharge. Raman spectroscopy is suitable option, because while IR or NIR spectroscopy is essentially based on illuminating the sample with a broad range of wavelengths of IR or NIR light and measuring which are absorbed, a Raman spectrum is obtained by illuminating the sample with a single wavelength of light from a laser and collecting and analysing the resulting scattered light. The features in the Raman spectrum corresponding to the various vibrational modes of a molecule are generally sharp, well resolved and, for many active pharmaceutical compounds, numerous. Additionally, Raman spectroscopy could be worked together with IR spectroscopy, in a more complex system, since the information collected from both techniques is complementary.

The suitable analytical tool chosen must take into account the small percentage of the components in the formulation, the chemical structure of the active substances to be detected and the acceptance limits established by guidances.

REFERENCES

[1] *Draft Guidance for Industry, Process Validation: General Principles and Practices*; U.S. Department of Health and Human Services, CDER, CBER, CVM, CGMP; Food and Drug Administration; Rockville, Maryland (November 2008).

[2] Federal Food, Drug and Cosmetic Act; US Code Section number 21; Chapter V (Drugs and Devices), Section 501 (Adulterated Drugs and Devices); http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/FDCActChapterVDrugsandDevices/ucm108055.htm

[3] Helle, M.R., Yliruusi, J., Mannermaa, J.P.; *A Literature Review of Pharmaceutical Process Validation*; Pharmaceutical Technology Europe; (March 2003).

[4] Shadle, P.; *Overview of GMPs*; BioPharm International; (November 15, 2004); http://biopharminternational.findpharma.com/ , consulted in June 2009.

[5] Federal Food, Drug and Cosmetic Act; US Code Section number 21; Chapter V (Drugs and Devices), Section 505 (New Drugs); http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/FDCActChapterVDrugsandDevices/ucm108125.htm#amendment

[6] Nash, R.A., Wachter, A.H.; *Pharmaceutical Process Validation: Third edition, Revised and Expanded;* Marcel Dekker, Inc Edition; New York (2003).

[7] *Current Good Manufacturing Practices in Manufacturing, Processing, Packing and Holding of Human and Veterinary Drugs*, Federal Register 43 (190), 45085 and 45086, September (1978).

[8] Loftus, B.T.; *Process Validation*; Pharmaceutical Index; 42 (nr 11a); 1202-1205; (1980).

[9] EOQC, Section for Pharmaceutical and Cosmetic Industry 4th European Seminar: *Validation of Manufacturing Processes*, Geneva (1980).

[10] *Guidelines on General Principles of Process Validation*; National Centre for Drugs and Biologics and National Centre for Devices and Radiological Health, Rockville MD; (1987).

[11] *Current Good Manufacturing Practices in Manufacturing, Processing, Packing and Holding of Human and Veterinary Drugs*, Federal Register 43, Parts 210 and 211; (1978, unless otherwise noted).

[12] *Current Good Manufacturing Practice for Finished Pharmaceuticals*, Federal Register 43, 45077; (1978).

[13] Code of Federal Regulations; *Title 21, Parts 210 and 211, Proposed Revisions*, Federal Register; (May, 1996).

[14] *Current Good Manufacturing Practice, Amendment of Certain Requirements for Finished Pharmaceuticals, Withdrawal;* Department of Health and Human Services; Food and Drug Administration (21 CFR Pats 210 and 211); Federal Register; Vol 72, Nb 232; (December 4, 2007).

[15] *Current Good Manufacturing Practice for Finished Pharmaceuticals*, Federal Register 60, 4901; (1995).

[16] *Current Good Manufacturing Practice for Finished Pharmaceuticals*, Federal Register 60, 4091; (1995).

[17] *Guide to Good Manufacturing Practice of Medicinal Products*; Revision 2; PIC/S Secretariat, Geneva (2001).

[18] Powell-Evans, K.; *Validation – Bad Manufacturing Practice?*; Pharmaceutical Engineering Europe; 10 (1); 29-30; (1998).

[19] *http://www.picscheme.org/pics.php*; consulted in April 2009.

[20] *Final Version of Annex 15 to the EU Guide to Good Manufacturing Practice – Qualification and Validation*; Working Party on Control of Medicines and Inspections; European Commission; (2001).

[21] *Note for Guidance on Process Validation*; CPMP/QWP/848/96; EMEA/CVMP/598/99; (2001).

[22] *Recommendations on Validation Master Plan, Installation and Operational Qualification, Non-sterile Process Validation Cleaning Validation*; Pharmaceutical Inspection Co-operation Scheme; (1999).

[23] *Australian Code of Good Manufacturing Practice for Medicinal Products*; Therapeutic Goods Administration; Health and Ageing Commonwealth Department; (2002).

[24] Branch, S.; *Guidelines from the International Conference on Harmonisation*; Journal of Pharmaceutical and Biomedical Analysis; Vol. 38; 798-805; (2005).

[25] Jatto, E., Okhamafe, A.; *An Overview of Pharmaceutical Validation and Process Controls in Drug Development*; Tropical Journal of Pharmaceutical Research; Vol 1 (2); 115-122; (2002).

[26] Chatterjee, B.; *Pursuing Pharmaceutical Quality and Economy*; BioPharm International; (June 2006); http://biopharminternational.findpharma.com/ , consulted in June 2009.

[27] Arling, E.; Beyond GMPs: The latest Approaches to Good Manufacturing Practices; Biopharm International; (November 15, 2004); http://biopharminternational.findpharma.com/ , consulted in June 2009.

[28] *Guidance ICH Q8 Pharmaceutical Development – Revision 1*; International Conference on Harmonization of Technical Requirements for the Registration for Pharmaceuticals for Human Use (ICH); (2009).

[29] *Guidance ICH Q9 Quality Risk Management*; International Conference on Harmonization of Technical Requirements for the Registration for Pharmaceuticals for Human Use (ICH); (2006).

[30] *Guidance ICH Q10 Pharmaceutical Quality System*; International Conference on Harmonization of Technical Requirements for the Registration for Pharmaceuticals for Human Use (ICH); (2009).

[31] Edwards, A.; *Quality Systems for Drugs and Biologics*; Pharmaceutical Technology (www.pharmtech.com); (February 2008).

[32] Garcia, T., Cook, G., Nosal, R.; *PQLI Key Topics – Criticality, Design Space, and Control Strategy*; Journal of Pharmaceutical Innovation; 3:60-68; (2008).

[33] Fraser, H.E.; *From Quality by Inspection to Quality by Design: A Roadmap for Success*; Pharmaceutical Technology (www.pharmtech.com); (September 2006).

[34] Joiner, B., Gaudard, M.; *Variation, Management and W. Edwards Deming*; Quality Progress; 29-37; (December 1990).

[35] US Food and Drug Administration; *Innovation and Continuous Improvement in Pharmaceutical Manufacturing: Pharmaceutical CGMPs for the 21st Century*; FDA; Rockville, MD; (September 2004).

[36] Somma, R., Signore A.; *Embracing Quality by Design*; Contract Pharmae; (October 2008); www.contractpharma.com, consulted in July 2009.

[37] Bush, L., *From CGMPs to the Critical Path: FDA Focuses on Innovation, Quality and Continuous Improvement: Inside and Out*; Pharmaceutical Technology; 28 (7); 34-44; (2004).

[38] United States Federal Drug Administration, "*The PAT Team and Manufacturing Science Working Group Report: A Summary of Learning, Contributions and Proposed Next Steps for Moving towards the "Desired State" of Pharmaceutical Manufacturing in the 21st Century*"; (2004);

http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4080b1_01_manufSciWP.pdf, consulted in September 2009.

[39] Hussain, A.; *Emerging Science Issues in Pharmaceutical Manufacturing: Process Analytical Technologie* - ACPS Meeting Presentation; The ACPS's Process Analytical Technology Subcommittee; (2001);

http://www.fda.gov/ohrms/dockets/ac/01/briefing/3804b1_07_hussain/sld001.htm

[40] Hussain, A.; *The Subcommittee on PAT: Overview and Objectives. PAT Subcommittee of the Advisory Committee for Pharmaceutical Science Meeting Presentation*; (2002);

http://www.fda.gov/ohrms/dockets/ac/02/briefing/3841b1_01_HUSSAIN/sld001.htm

[41] Davies, B., Ellis, S.; *The Route to Process Understanding and Control*; Pharmaceutical Technology Europe; August 2005;

http://pharmtech.findpharma.com/pharmtech/Analytical/The-Route-to-Process-Understanding-and-Control/ArticleStandard/Article/detail/173523, consulted in June 2009.

[42] Greb, E.; *A Propitious Period for PAT?*; Pharmaceutical Technology; November 2008; http://pharmtech.findpharma.com/pharmtech/Analytics/A-Propitious-Period-for-PAT/ArticleStandard/Article/detail/565184, consulted in June 2009.

[43] *PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*; U.S. Department of Health and Human Services, CDER, CBER, CVM, CGMP; Food and Drug Administration; (September 2004).

[44] Calnan, N., Redmond, A., O'Neill, S.; *The FDA's Draft Process Validation Guidance – A Perspective from Industry*; Pharmaceutical Engineering; Vol. 29, nr 3; 8-16; (2009).

[45] Snee, R., Cini, P., Kamm, J., et al; *Quality by Design – Shortening the Path to Acceptance*; Pharmaceutical Processing; www.pharmpro.com, consulted in June 2009.

[46] Nosal, R., Schultz, T.; *PQLI Definition of Criticality*; Journal of Pharmaceutical Innovation; 3:69-78; (2008).

[47] Lepore, J., Spavins, J.; *PQLI Design Space*; Journal of Pharmaceutical Innovation; 3:79-87; (2008).

[48] Davis, B., Lundsberg, L., Cook, G.; *PQLI Control Strategy Model and Concepts*; Journal of Pharmaceutical Innovation; 3:95-104; (2008).

[49] Kamm, J., Cini, P.; *Predictive Modelling: Putting ICH Guidelines to Work in Process Validation*; Pharmaceutical Technology Europe; 34-38; (March 2009).

[50] Xie, L., Wu, H., Shen, M., et al; *Quality-by-Design: Effects of Testing Parameters and Formulation Variables on the Segregation Tendency of Pharmaceutical Powder Measured by the ASTM D 6940-04 Segregation Tester*; Journal of Pharmaceutical Sciences; Vol 97; no 10; 4485-4497; (2008).

[51] Process Validation Report, 2005, LM

[52] Extended Evaluation Capsules Analytical Data, 2005, LM

[53] Characterization and Registration Report, 2006, LM

[54] Finished product raw data, LM, 2008.

[55] Stark, J.; A Few Words about FMECA; John Stark Associates Management Consultants; www.johnstark.com/fwfme.html, consulted on June 2010.

[56] Raw Material raw data, LM, 2008.

[57] Technical documentation on Paracetamol from Mallinckrodt, assigned in December 2009.

[58] Process Validation Report, 2007, LM

[59] Technical documentation on Pseudoephedrine HCl from BASF, assigned in May 2009.

[60] Figueiredo, Joana; *FT-NIR spectroscopy and Laser Diffraction particle sizing of API's in Pharmaceutical formulations*; Dissertation for Master Degree in Chemical

Engineering; Instituto Superior Técnico, Universidade Técnica de Lisboa; (September 2008).

[61] *Guidance for Industry – Powder Blends and Finished Dosage Units – stratified in-process dosage – Unit sampling and Assessment*, FDA, 2003.

[62] Webster, S., Baldwin, K.; *Raman Spectroscopy for Pharma - Principles and Applications*; Pharmaceutical Technology; 2005.

[63] Webster, S., Baldwin, K.; *Raman as a PAT Tool*; Pharmaceutical Technology; 2005.

[64] Ciurczak, E.; *A Spectroscopy Guide for PAT*; Pharmaceutical Manufacturing Magazine; 2008.

[65] *FMECA index tables for severity, occurrence and detection*; Academic material assigned in Quality Management Systems classes of Master on Pharmaceutical Engineering (Instituto Superior Técnico, Universidade Técnica de Lisboa / Faculdade de Farmácia, Universidade de Lisboa); 2009.

ANNEX 1 – FMECA TABLES [65]

Severity index table

Criteria	Impact on product quality	Ranking
Not relevant	Minimal effect	1
The failure mode may have some effect on product's quality	The failure mode is not detected by quality tests	2
Not important	Minor effect	3
The failure mode may cause some relevant effect on product's quality	The failure mode probably will not be detected or cause any deterioration in product's quality	4
Intermediate	More relevant effect	5
The failure mode may compromise product's quality	The failure mode causes deterioration on product's quality	6
Severe	Critical effect	7
The failure mode compromises seriously product's compliance.	High deterioration on product's quality, without safety or legal requirements being compromised.	8
Very significant	Safety	9
The failure mode compromises product's quality and patient's safety.	The product is not within compliance and or quality registered requirements.	10

Occurrence index table

Criteria	Ranking	Probability of ocorrence
Low probability of occurrence The capacity indicates ± 5σ within specifications. Cpk ≥ 1,67	1	< 1 in 1000 000
Very low probability of occurrence Process under statistic control. The capacity indicates ± 4 σ within specifications. Cpk ≥ 1,33	2	1 in 20000
Low probability of occurrence Process under statistic control. The capacity indicates ± 3,5 σ in specifications. Cpk ≥ 1,00	3	1 in 4000
Average probability of occurrence Process under statistic control. The capacity indicates ± 3 σ within specifications. Cpk ≤ 1,00	4 5 6	1 in 1000 1 in 400 1 in 80
High probability of occurrence Process out of statistic control	7 8	1 in 40 1 in 20
Very high probability of occurrence It is almost certain that the failure mode occurs	9 10	1 in 8 1 in 2

Detection index table

Criteria	Ranking
Very high capacity of detection. The controls always detect the existence of the failure mode. The probability of detection is not less than 99,99%.	1 2
High capacity of detection. The controls have a high probability of detection of the failure mode. The probability of detection is not less than 99,8%.	3 4
Average capacity of detection. The controls may detect the failure mode. The probability of detection is not less than 98%.	5 6
Low capacity of detection. The controls have a low capacity to detect the failure mode. The probability of detection is not less than 90%.	7
Very low capacity of detection. The controls may not detect the failure mode. The probability of detection is less than 90%.	8
No capacity of detection. The controls will not detect the failure mode. The failure mode can be ignored in quality evaluation.	9 10